IRIS Document

Pyrene	1987/12/01	Key Study Document	6
Chemical Name	Document Date YYYY MM DD	File Descriptor	Sequence #

IRIS FILE TYPE

Circle One → (IRIS Chemical File) | Public Submission | RfD/RfC & CRAVE Files

Subtype

Circle One

- Decision files for chemicals listed in IRIS
- Toxicological Review
- Peer review Record
- (Key/difficult to find materials)
- Other

Chemical nominations | New Information | Other

CRAVE files prior to 1995 | Non-decisional file reference and supplemental date prior to 1997 | Other

Key Study - "13-Week Mouse Oral Subchronic Toxicity Study"

Description

Dynamic Corp.

Organization

Author

Scan Date

TRL Study #042-012

Conducted for:

DYNAMAC CORPORATION
11140 Rockville Pike
Rockville, Maryland 20852

by:

TOXICITY RESEARCH LABORATORIES, LTD.
510 West Hackley Avenue
Muskegon, Michigan 49444

13 Week Mouse Oral Subchronic Toxicity Study

Compound:

Pyrene

Start of Test (pretreatment):	August 24, 1987
Start of Dosing:	August 31, 1987
Final Sacrifice Date:	November 30, December 1 and 2 1987

Summary

The objective of this study was to evaluate the toxicity of Pyrene in a subchronic toxicity study.

Four groups of male and female CD-1 mice (20/sex/group) were placed on study with extra satellite (5/sex/group) mice. A fifth group (Group V mice-30/sex) was placed on study for baseline blood evaluations.

Groups I, II, III, IV were dosed with 0 (control), 75,125 and 250 mg/kg/day of pyrene respectively for 13 weeks. The pyrene was diluted to the proper concentrations in corn oil vehicle. Satellite animals were dosed for 14 days only.

The mice were observed twice daily for clinical signs. Body weights and food consumption values were reported weekly. Hematologic and serum chemistry evaluations were completed during the pretest period (Group V) and during week 14 (at final sacrifice). At final sacrifice gross post-mortem examinations were completed, organ weights were taken and histologic examinations were subsequently done on the tissues collected.

Conclusion

Pyrene given orally to mice for 13 weeks caused compound-related effects in all treated dose levels (75, 125, and 250 mg/kg/day). No compound-related mortality could be attributed to pyrene administration during this study.

The compound related effects seen in the low dose group (75 mg/kg/day) were limited to mildly increased total food consumption (females only) and mildly reduced total weight gains which in combination produced increased food conversion ratios. Hematology evaluation yielded minor numerical decreases in RBC, PCV and HGB values in male mice only. Compound related statistically significant decreases in absolute and relative kidney weights (males) were noted. Corresponding lesions of renal tubular regeneration (nephropathy) were noted on histopathologic evaluation. Nephropathy was noted in 4 of 40 mice (10.0%) of this group with severity ranging from minimal to mild. Absolute liver weights were found to be mildly increased in both sexes with female mice possessing increases in relative liver weights also.

Mid dose (125 mg/kg/day) mice had compound-related effects limited to significantly elevated food consumption (Study week 8, female mice) and increased total food consumption (females) and slighty decreased total weight gain (males and females). Food conversion ratios were therefore increased above control values. Group III male mice also had numerical decreases in RBC, PCV and HGB values. Male mice also had significant decreases in serum albumin at the week 14 evaluation. Significant decreases in absolute and relative kidney weights were noted. Microscopic lesions of renal tubular regeneration were noted in 8 of 40 mice (20.0%) of this group. Severity of this lesion ranged from minimal to mild. Absolute and relative liver weights were increased in mice of both sexes.

Study Group IV (250 mg/kg/day) female mice had compound-related significant food consumption increases during 5 of the 13 weeks on study with increased total food consumption. Total food consumption was dramatically increased (13.1%) in female mice compared to a lesser effect in males (2.7%). Mice of both sexes had reduced total weight gains causing increased food conversion ratios. Statistically significant decreases in RBC, PCV and HGB values were seen in male mice of

Study Group IV with females exhibiting only slight decreases in these parameters. Male mice had significant decreases in serum albumin at the week 14 evaluation. Highly significant decreases in absolute and relative kidney weights were seen in both male and female mice. Renal tubular regeneration (nephropathy) was evident in 19 of 40 mice (47.5%) of this group. Severity of the nepropathy from minimal to mild. Statistically significant increased absolute liver weights were seen in female mice of this group with numerically increased absolute liver weights observed in the male population. Relative liver weights were significantly increased in mice of both sexes.

Due to the pyrene effects seen in the 75 mg/kg/day dose level it must be concluded that the no effect dose level is less than 75 mg/kg/day.

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I. Introduction

The purpose of this study was to evaluate the toxicity of pyrene in a mouse subchronic toxicity study.

This study was conducted in accordance with the protocol (Appendix A), the Standard Operating Procedures of Toxicity Research Laboratories, Ltd. (TRL)1, and in compliance with Good Laboratory Practice Regulations, Nonclinical Laboratory Studies.2 In addition, the study was performed in accordance with the EPA Pesticide Assessment Guidelines, Subdivision F, Section 158.82-1 and the EPA Toxic Substance Control Act Testing Guidelines for Ninety Day Subchronic Toxicity Studies (40 CFR 798.2650)2. Procedures pertinent to this study are described herein.

II. Methods

A. Test Material

The test material, pyrene, is a polycyclic aromatic hydrocarbon with a molecular weight of 202.26. The test material Lot No. DTO1816ML, Batch No. 01, was supplied

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1 Revised, March 1, 1985
2 Federal Register, Volume 48, Number 230, Part III, November 29,1983, pp. 53922-53944
3 Midwest Research Institute., 425 Volker Boulevard, Kansas City, Missouri 64110

by the Midwest Research Institute3 on July 8, 1987, and was stored at room temperature. Stability and purity were previously established by Midwest Research Institute (Appendix B.). The bulk test material has been identified by ultraviolet/visible and nuclear magnetic spectroscopy, mass spectroscopy, and differential scanning calorimetry. Purity was established by means of thin-layer and gas chromatography and was found to be greater than 98% pure. Samples of dosing solutions (30 ml of 0, 7.5, 12.5, 25.0 mg/ml concentrations), the corn oil vehicle (50 ml), and a bulk sample (5 grams) were taken for gas chromatograph analysis on August 24, September 22, and November 18, of 1987. The results of the analyses are located in Appendix C.

B. Animals and Husbandry

1. Test System

The CD-1 mouse was chosen as a test system because of its established usefulness in toxicologic studies and as a pharmacologic model. The oral route of administration was chosen because this will be the probable route of human exposure.

On August 17, 1987, 156 male and 156 female weanling CD-1 Charles River Laboratories mice arrived in the laboratory.[4] A quarantine period of 7 days prior to initiation of the pretreatment week was allowed. During the quarantine period, the mice were observed with respect to general health and physical appearance. No evidence of physical or clinical signs of disease were observed in these mice. Four male and three female mice with ocular abnormalities were discarded at the ophthalmic examination conducted during the quarantine period. At the end of the quarantine period, 152 male and 153 female mice were available for potential placement on study. Mice of these groups were assigned to dose groups using a computer generated randomization schedule.[5] Minor adjustments to group assignments were made to insure similar initial group mean body weights (ten mice were reassigned).

Each mouse was individually identified by toe clip and was given a unique permanent animal number. Mice were further identified by a color-coded cage card listing

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4 Mice were supplied by Charles River Laboratories., Shaver Road, Portage, Michigan 49444

5 Randomization tables produced on September 5, 1987, by John Quiring, Ph.D., Biostatistician

study number, animal number, sex, group, compound, and dose level. Recording of weekly body weight and food consumption began on August 24, 1987 (first day of pretreatment).

2. Environmental Conditions

The mice were housed individually in suspended metal wire-bottom cages.6 During the quarantine period, the mice were housed 3/cage. A clean/dirty corridor system was in effect. Room air was filtered, environmental humidity (average 57.38 ± 12.90%)7 and temperature (average 73.52 ± 0.55°F)7 were controlled. The temperature value was calculated using the daily high and low values, ±1 standard deviation. One value per day was used to calculate the humidity average. A 12-hour light/dark cycle was controlled automatically. Filtered municipal water8 and Purina Certified Rodent

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6 Mice were housed in accordance with recommendations contained in DHHS Publication No. 85-23 (NIH): Revised 1985, "Guide for the Care and Use of Laboratory Animals."

7 ± Standard Deviation

8 Water used at TRL is analyzed periodically for the presence of contaminants as defined by the Environmental Protection Agency "National Interim Primary Drinking Water Regulations" Code of Federal Regulations, Title 40-Protection of Environment Part 141.11 (b) and 141.12.

Chow #50029 (pellet) were available ad libitum. Rodent Diet Composition is located in Appendix D.

C. Compound Administration

The doses selected for this study are 0, (Corn oil vehicle - Study Group I), 75 mg/kg/day (Study Group II), 125 mg/kg/day (Study Group III), 250 mg/kg/day (Study Group IV) of pyrene.

Study Group	Concentration(mg/ml)	Dose Level (mg/kg/day)
I	0	Vehicle Control
II	7.5	75
III	12.0	125
IV	25.0	250
V	Baseline blood evaluation	

Study Group V was utilized for baseline blood evaluation. Administration of the test material began on August 31, 1987. The mice scheduled for the final necropsy were dosed for 92, 93 or 94 days. The mice

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9 Lot #s May-29-87-1A, July-21-87-1D. Checkerboard Square, St. Louis, Missouri 63164. This feed has been tested by the manufacturer for contaminants, none of which were present at levels that would be expected to affect the outcome of this study. Rodent Diet Composition is located in Appendix D.

were assigned to groups and dosed as follows:

	Male		Female	
Group	Final Sacrifice	Satellite[10]	Final Sacrifice	Satellite[10]
I	001-020	021-025	026-045	046-050
II	051-070	071-075	076-095	096-100
III	101-120	121-125	126-145	146-150
IV	151-170	171-175	176-195	196-200
V[11]		201-230		231-260

The amount of test material administered was based on the most recently recorded individual body weight value. Fresh dosing solutions were prepared approximately every two weeks by suspending the compound in corn oil at concentrations of 7.5, 12.5, and 25.0 mg/ml. Solutions were dosed orally (via a gastric gavage) at a volume of 10 ml/kg of body weight. Control mice (Group I) received corn oil at the same dose volume. Each mouse was dosed via oral gavage using a 1.0 cc plastic syringe and a 20 gauge ball-tipped metal dosing cannula.

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10 Five male and five female mice were assigned as satellite animals and were dosed for 14 or 15 days. These mice were subsquently sacrificed. These were backup animals to be placed on study in the case of technical problems.

11 Study Group V mice are for baseline blood evaluations only.

D. Clinical Observations

Body weights and food consumption were recorded weekly. The mice were observed for mortality and/or overt signs of toxicity once daily during the pretreatment period and three times daily after the initiation of dosing. Clinical observations were recorded prior to dosing, within one hour of dosing, and at least six hours later or when any unusual symptoms are noted.

E. Ophthalmology

All mice received funduscopic (indirect binocular ophthalmoscopy) examination during the pretreatment period and Study Week 13 by a veterinary ophthalmologist.[12]

F. Clinical Laboratory Studies

1. Sampling

Baseline blood evaluations were done on mice of Study Group V on August 25, 1987. Blood was collected from the posterior vena cava of CO_2 anesthetized non-fasted mice for baseline evaluation (Study Group V), and at final necropsy (Study Groups I through IV).

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12 Performed by E.L. Kuhns, D.V.M., 2426 Boulevard Drive, S.W., Wyoming, Michigan 49509 (pretreatment) and G. Blanchard, D.V.M., Michigan State University, East Lansing, Michigan (terminal exam).

2. Tests Performed

Baseline hematology was conducted on the first ten (numerical) males and females of Study Group V. The second ten (numerical) males and females of Study Group V received the serum chemistry test listed below and indicated by (*). The third ten (numerical) males and females of Study Group V received the remaining serum chemistry test. At final sacrifice the hematology evaluations and serum chemistries (indicated by *) were run on the first ten (numerical) surviving males and females of Study Groups I through IV. The remaining serum chemistry test were run on the second ten surviving males and females of these study groups.

Hematology:

Erythrocyte count (RBC)
Total and differential leukocyte counts (WBC)
Hemoglobin (HGB)
Erythrocyte packed cell volume (PCV)
Mean cell volume (MCV)
Mean cell hemoglobin (MCH)
Mean cell hemoglobin concentration (MCHC)

Serum Chemistry:

Glucose (GLUC)*
Urea Nitrogen (BUN)*
Cholesterol (CHOL)
Total bilirubin (TOT BILI)*
Total protein (TP)*
Albumin (ALB)*
Globulin (GLOB; calculated)*
A/G ratio (calculated)*
Alkaline phosphatase (ALK PHOS)*

Serum glutamate oxalacetate transaminase (SGOT)*
Serum glutamate pyruvate transaminase (SGPT)*
Lactate dehydrogenase (LDH)
Sodium (Na)
Potassium (K)
Chloride (Cl)
Total carbon dioxide (TCO_2)

G. Necropsy

Gross postmortem examinations were performed on all mice at final sacrifice (excluding mice of Study Group V and satellite animals) and those which died during the course of this study. On study days 92, 93 or 94, all surviving mice were sacrificed and necropsied. The mice sacrificed were anesthetized with CO_2 and exsanguinated by cardiac puncture. The external surface, all orifices, the cranial cavity, external surface of the brain, the thoracic, abdominal and pelvic cavities and their viscera, and the tissues and organs of the neck region were examined. Any gross lesions observed were recorded. Organs and tissues listed in Section II paragraph H. were removed from each animal and preserved. Lungs were inflated with 10% neutral buffered formalin via the trachea (except for animals found dead). Eyes with optic nerves from all mice killed at the final sacrifice were preserved in Russell's fixative. The testes and epididymides from all male mice were preserved in Bouin's fixative.

All other tissues were preserved in 10% neutral buffered formalin. The feet were saved with the tissues of each mouse for positive identification.

The brain, heart, liver, spleen, kidneys, and testes were weighed prior to fixation, at the final necropsy.[13] For paired organs, the organ weight was the combined weight of right and left members of the organ pair. Organ to body weight ratios were calculated. No organ weights were taken on mice found dead.

H. Histology

A microscopic examination of hematoxylin and eosin stained paraffin sections of the tissues listed below was performed on all control and Study Group IV mice from the final sacrifice, and on those mice found dead. A microscopic examination was performed of stained bone marrow smears from the femurs of mice of Groups I and IV (also female mouse #140 of Study Group III, found dead). In addition the livers, lungs, and kidneys of Study Group II and III mice and any tissue with a gross lesion seen at necropsy, were also examined

13 Adrenals and ovaries were not weighed at final necropsy as required by the protocol due to an oversight.

microscopically. The following tissues were fixed and preserved for all mice (except Study Group V and satellite animals) and subsequently examined histologically for those animals described above:

Adrenals
Aorta (longitudinal section)
Bone with marrow and joint- femur
Brain (three levels)
Cecum
Colon
Duodenum
Epididymides
Esophagus
Eyes with optic nerve
Gallbladder
Heart
Ileum
Jejunum
Kidneys
Liver
Lungs with bronchi
Mammary gland
Mesenteric lymph node
Thyroids with parathyroids
Urinary bladder
Uterus
Ovaries
Pancreas
Pituitary gland
Prostate
Rectum
Salivary gland (mandibular)
Sciatic nerve
Seminal vesicles
Skeletal muscle (thigh)
Skin
Spinal cord (cervical, thoracic, and lumbar)
Spleen
Sternum
Stomach (forestomach, cardiac, fundic and pyloric regions)
Testes
Thymus
Trachea
Any other tissues with gross lesions

Fixed tissues of 160 mice from the final sacrifice groups were sent to Pathology Associates, Inc. for processing.[14] Six found dead mice (No. 068, 079, 094, 110, 141, and 145) had been processed at TRL, the slides from these mice were subsequently examined by Pathology Associates, Inc. (PAI) The tissues of found dead mice were trimmed, processed, embedded, sectioned and stained according to the TRL Histology Department Standard Operating Procedures.

All other tissues required by the protocol and all gross lesions from the 80 mice in Study Groups I and IV and one found dead mouse No. 062 of Study Group II were processed through paraffin, sectioned at approximately 6 microns, stained with hematoxylin and eosin, and examined histologically at PAI. For the remaining 73 mice in Study Groups II and III no target tissues were designated. The livers, lungs, kidneys, and gross lesions were processed in the same manner and examined after all of the tissues in Study Groups I and IV were examined.

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14 Pathology Associates, Inc., 10075 Tyler Place, Hyatt Park II, Ijamsville, Maryland, 21754.

At the histologic examination, some lesions were graded, when necessary, using the following system: minimal, mild, moderate, and marked. Lesions were not graded when, in the judgment of the pathologist, grading would not contribute to the evaluation of the toxicologic potential of the test material.

I. Statistics

The data were tested for homogeneity of variance by Bartlett's method.15 If the data were found to be homogeneous, differences between control (Group I) and treatment group means were tested for statistical significance by the method of Dunnett16. If the data were found not to be homogeneous, the method of Gill17 (modified Dunnett's) was employed.

J. Data Retention

All data, including slides, blocks, wet tissues, and a copy of this report will be returned to the sponsor and

15 Snedecor, G.S., and Cochran, W.G. (1967). Statistical Methods, 6th ed.,Iowa State University Press, Ames, Iowa.

16 Dunnett, C.W. (1964). New tables for multiple comparison with a control. Biometrics, 20:482-491.

17 Gill, J.L. (1977). Dairy Sci. 60:444-449

stored at the sponsor's facility archives, Dynamac Corporation, 11140 Rockville Pike, Rockville, Maryland 20852.

III. Results

A. Mortality

Seven mice (No.s 062, 068, 079, 094, 110, 141, and 145) scheduled for the final sacrifice died during the course of the study, on study days 75, 10, 10, 12, 14, 14 and 10 respectively. The distribution of mortality is provided in the following table:

Distribution of Mortality

Study Group	Dose(mg/kg/day)	Males	Females
I	0	0	0
II	75	2	2
III	125	1	2
IV	250	0	0

Due to the distribution of mortality and the subsequent gross and histopathologic examination results, the early deaths were not attributed to compound administration.

B. Clinical Signs

Incidence of clinical signs are listed in Table 1.

Salivation was the only pyrene related clinical sign seen during the course of this study. With one exception, the salivation was seen exclusively in the treated groups and was usually seen at the 0-1 hr post dose observation interval. Dose dependent progressions were generally not evident.

The other clinical signs observed during this study are commonly seen in laboratory mouse populations. The effects included: axillary mass, superficial wound, atrophy eye, swollen penis, inguinal mass, hypoactivity and unkempt appearance. Additional signs of urine wet abdomen, exophthalmos, alopecia, labored respiration, pale, hypothermia, and death were also seen. These signs were seen at a relatively low incidence and the distribution of these signs did not reflect a causal relationship with pyrene administration.

C. Food Consumption and Body Weight

Food consumption averages, body weight averages and weight changes are listed in Table 2. Individual body weights and individual food consumption values are listed in Appendix E and F.

Statistically significant, compound-related food consumption increases were seen in female mice of Study Groups III (125 mg/kg/day) and IV (250 mg/kg/day). Study Group IV female mice attained statistical significance levels of $P \leq 0.01$ during Study Weeks 8, 10 and $P \leq 0.05$ during Weeks 3, 4, and 9 respectively. Group IV female mice consistently had mean food consumption values that exceeded control values at all intervals throughout the study, which was reflected in total food consumption values to exceed that of controls by 13.1%. Study group III food consumption values were increased significantly ($P \leq 0.05$) only during Study Week 8. Total food consumption values for treated female mice (Study Groups II, III and IV) exceeded control values in a dose dependent pattern.

No statistically significant effects were noted on the food consumption of male mice during any interval of this study. Study Group IV (250 mg/kg/day) male total food consumption values did exceed control values but only by 2.7%.

The percent increase in total food consumption are listed below:

Percent Increase in Total Food Consumption

Compared to Controls

Group	Dose (mg/kg/day)	Males	Females
I	0	-	-
II	75	-4.6%	1.2%
III	125	-1.3%	5.6%
IV	250	2.7%	13.1%

Two instances of significant ($P \leq 0.05$) reduced food consumption were noted in Study Group II (125mg/kg/day) males during Study Weeks 8 and 10. This reduced consumption was considered to be due to random variation and not an effect of pyrene.

No statisistically significant deviations were seen in body weights of male or female treated mice. It should be noted that total weight gains for treated male and female mice were consistently less than controls, but a clearly defined dose-response relationship was not evident.

Food conversion ratios depict a compound related negative effect on food conversion efficiency of treated mice. The increased ratios of female mice did represent a dose-reponse relationship, but the ratios of male mice did not indicate dose dependency. The

effect appears to be a reflection of the increased food consumption (Group III and IV female mice) coupled with relatively lower total weight gains seen in all the treated groups.

The food conversion ratios are listed below:

Food Conversion Ratios

(grams of food consumed/ gram of body weight gained on study)

Group	Dose (mg/kg/day)	Males(gms)	Females(gms)
I	0	65.2	78.1
II	75	82.0	86.2
III	125	79.4	87.9
IV	250	79.2	94.2

D. Ophthalmology

Ophthalmoscopic examinations were performed on all mice during the pretreatment week and week 13 of the study . Seven mice that had eye lesions at the pretreatment evaluation were not included for possible placement on the study.

Three ocular abnormalities were found at the Week 13 examination. The abnormalities found included: Female mouse #033 of Study Group I (0 mg/kg/day) had an iris

prolapse and phthisic left eye, Female mouse #042 of Study Group I had ocular atrophy of the left eye and Female mouse #129 of Study Group III (125 mg/kg/day) had a central corneal epithelial dystrophy of the left eye.

In consideration of the distribution and the nature of the observed lesions a causual relationship with the compound is not apparent.

E. Clinical Pathology

Hematology

Hematology Summary and Hematology Values are listed in Table 3 and Table 5 respectively.

Statistically significant ($P \leq 0.01$) compound related decreases in red blood cell numbers (RBC), packed cell volumes (PCV), and hemoglobin (HGB) levels of high dose (Study Group IV, 250 mg/kg/day) male mice were noted at the Study Week 14 hematology evaluations. Mean RBC, PCV and HGB levels of male Study Group IV mice were 90.4, 89.8 and 90.2% of control (Study Group I, 0 mg/kg/day) levels respectively.

Apparent trends toward lower RBC, PCV and HGB values were also seen in male mice of the mid dose group (Study Group III, 150 mg/kg/day), and the low dose group (Study Group II, 75 mg/kg/day). Theses values were reduced numerically below control levels and statistical significance was not achieved, although dose dependency was apparent.

Female Study Group IV mice did have relatively lower RBC, PCV and HGB levels than their controls. Group IV females had RBC, PCV and HGB values that were 94.7, 95.0, and 95.8% of control values respectively. Although these values were slightly lower, statistical significance was not achieved.

Other hematology parameters that did attain statistical significance at the Study Week 14 evaluation but were considered unrelated to compound adiministration were: Group II (75 mg/kg/day) female mice had significant ($P \leq 0.01$) decreases in RBC numbers and significant ($P \leq 0.05$) increases in mean corpuscular volumes (MCV) values.

Serum Chemistry

Serum Chemistry Summary and Serum Chemistry Values are listed in Tables 4 and 6 respectively.

Compound-related decreases in albumin levels were seen at the Week 14 (final necropsy) serum chemistry evaluation.

Specifically, Study Group IV (250 mg/kg/day)and III (125 mg/kg/day) male mice had statistically significant ($P \leq 0.05$) decreases in serum albumin levels when compared to controls. Albumin values for male mice of Study Groups III and IV were 91.9% of control values. Female mice of all treated groups had albumin values similar to control levels.

Other serum chemistry parameters that did attain statistical significance but were considered not related to compound administration were: Study Group III (150 mg/kg/day) female mice had significant ($P \leq 0.05$) decreases in total bilirubin and increased serum cholesterol values, Group IV (250 mg/kg/day) females had significantly ($P \leq 0.05$) elevated serum chloride values.

F. Gross Pathologic Observations

Gross Pathologic Observations are listed in Table 7.

Compound-related gross pathologic observations were not seen during this study. The lesions seen at necropsy were found in relatively low incidence and dose-dependant patterns were not present.

The gross pathologic lesions seen included: swollen penis and enlarged spleen, and uterus. Other gross pathologic observations seen were masses of the skin, subcutaneous neck region, and a superficial wound of the skin. These lesions are considered to be random lesions found commonly in laboratory mouse populations.

G. Organ Weights

Relative and Absolute Organ Weights are listed in Table 8.

Statistically signifiant ($P \leq 0.01$) decreases in absolute kidney weights were found in male and female mice of Study Group IV. Significant ($P \leq 0.01$) decreases in absolute kidney weights were also noted in male mice of Study Group II and III. Female mice of Study Group III did have decreased absolute kidney

weights but attained significance levels of only $P \leq 0.05$. These absolute kidney weight decreases generally reflect dose dependency in the treated groups (with the exception of Group II males).

The percent decrease in absolute kidney weights in comparison to control kidney weights are listed below:

Percent Decrease in Absolute Kidney Weights Compared to Controls

Group	Dose (mg/kg/day)	Males	Females
I	0	-	-
II	75	14%	7%
III	125	14%	9%
IV	250	20%	11%

Treated male mice of Study Group III (125 mg/kg/day) and IV (250 mg/kg/day) also had highly significant ($P \leq 0.01$) compound related decreases in relative kidney weights when compared to controls. Males of Study Group II (75 mg/kg/day) also had significant decreases but to a lessor extent ($P \leq 0.05$). Female mice of Study Groups IV and III had significant decreases in relative kidney weights to levels of $P \leq 0.01$ and $P \leq 0.05$

respectively. The percent decrease in relative kidney weights are listed below:

Percent Decrease in Relative Kidney Weights Compared to Controls

Group	Dose (mg/kg/day)	Males	Females
I	0	-	-
II	75	11%	6%
III	125	11%	13%
IV	250	16%	13%

Pyrene administration caused increased absolute and relative liver weights in all treated groups of both sexes (with one exception, Study Group II, 75 mg/kg/day male absolute liver weights were lower than controls). These increases generally suggested dose dependency. Statistically significant ($P < 0.01$) increases were seen in Study Group IV (250 mg/kg/day) female mouse absolute liver weights.

The percent increase in absolute liver weights over control liver weights are listed below:

Percent Increase in Absolute Liver Weights Compared to Controls

Group	Dose (mg/kg/day)	Males	Females
I	0	-	-
II	75	-4%	7%
III	125	3%	11%
IV	250	6%	16%

Relative liver weights were found to be significantly ($P \leq 0.01$) increased in male and female mice of study Group IV and only female mice of study Group III. The percent increase in relative liver weights are listed below:

Percent Increase in Relative Liver Weights Compared to Controls

Group	Dose (mg/kg/day)	Males	Females
I	0	-	-
II	75	0%	8%
III	125	6%	13%
IV	250	10%	19%

No other significant effect was observed in absolute or relative organ weights.

H. Histopathology

The incidence of histopathologic lesions are listed in Table 10. Individual mouse reports are listed in Appendix H. The complete report of histopathologic findings submitted by Pathology Associates, Inc. is found in Appendix I.

Seven mice died prior to final sacrifice, the cause of death was considered unrelated to compound administration. The gross necropsy findings and/or microscopic lesions of mice #068, 079, 094, 110 and 145 indicated the deaths apparently resulted from gavage error. The cause of death of mouse #062 was the result of erythrocytic leukemia. Mouse #141, the cause of death could not be determined from gross necropsy findings or histopathologic examination.

No early deaths were seen in the high dose group (Study Group IV, 250 mg/kg/day).

Pyrene-related effects were apparent in the incidence of nephropathy of both male and female mice. The nephropathy observed was characterized by the presence of multiple foci of renal tubular regeneration sometimes accompanied by interstitial lymphocytic infiltrates and/or foci of interstitial fibrosis.18 The severity of these lesions were minimal or mild. The incidence of this lesion did indicate dose dependency in female mice, with the Study Group IV incidence five times that of the controls. This progression was not present in the males, nor was the difference in incidence between Study Group IV and controls as dramatic. However, the incidence of nephropathy in Study Group IV males was double that of controls. The incidences are listed below:

Incidences of Nephropathy

Group	Dose (mg/kg/day)	Males	%	Females	%
I	0	4/20	20%	2/20	10%
II	75	1/20	5%	3/20	15%
III	125	1/20	5%	7/20	35%
IV	250	9/20	45%	10/20	50%

18 Interstitial lymphocytic infiltrates found in the absence of tubular changes were not included in the heading nephropathy, but were listed separately.

In some mice interstitial lymphocytic infiltrates were seen in the absence of tubular changes and were considered not related to pyrene administration. The incidence of this was not indicative of dose dependency and is not an uncommon finding in laboratory mice.

Histopathologic examination of other tissues yielded no other treatment-related lesions. Lung lesions of one or more foci of mixed inflammatory cells within the interstitium (inflammation) were found in mice of all Study Groups in relatively normal distributions. Some of these lungs (and some without the interstitial foci) also contained one or more foci of lymphocytic infiltrates in perivascular or paravascular distribution. The presence of mixed inflammatory cells is suggestive of exposure to infectious agents and is not compound related.

IV. Discussion

Oral administration of the pyrene to CD-1 mice over a period of 13 weeks produced salivation, deviations in food consumption, body weights and food conversion ratios. Other changes attributed to compound administration were; deviations in hematology (slight anemia) and serum chemistry parameters (serum albumin),

gross renal and hepatic organ weight changes, and renal morphological pathology (nephropathy). Pyrene caused no compound related mortality in this study.

The salivation seen was was limited to the treated mice (with one exception) and was generally observed at 0-1 hour post dosing observation interval only. Without a clearly defined dose-response relationship it may be inferred that this effect may be due to the physical presence of the compound in the dosing solution rather than a systemic toxicity.

Food consumption was positively affected by pyrene administration in female mice of Study Group IV (250 mg/kg/day) and to a lesser extent Study Group III (125 mg/kg/day). Food consumption values of male mice were not effected at any interval.

Body weights of treated groups as compared to control values were not found to be significantly different at any weekly interval. But a tendency toward lower total body weight gain was noted in both males and females of all treated groups.

The increased food consumptions, and generally lower weight gains of female treated mice did generate appreciably increased food conversion ratios. Treated male mice had increased ratios due solely to the decreased total weight gains. These increases are probably a manifestation of decreased food conversion efficiency due to compound administration.

Treated male mice had hematologic changes due to pyrene administration. Treated male mice had an inclination toward lower red blood cell numbers (RBC), packed cell volumes (PCV), and hemoglobin (HGB) values than controls. This effect was found to be statistically significant in males of Study Group IV with only numerical reductions in Groups III and II. Female mice of Study Group IV had only minimal numerical reductions in these parameters.

The lower RBC, PCV and HGB values with MCV and MCHC values relatively similar to controls suggest tendency toward a normalcytic normochromic anemia. The concurrent absence of reticulocytosis, polychromasia or morphologic changes on histopathologic evaluation of the bone marrow indicate no apparent response of the bone marrow to the slightly anemic state and conveys a

nonregenerative impression. Nonregenerative anemias are generally due to diminished bone marrow erythropoiesis. These reductions, although statistically significant, may represent only minimal significance in a biological sense. The decreased values of the high dose male mice are not outside the baseline parameters for mice of this sex, age, or breed (see Appendix K).

Generally, significant (often to a high degree) reductions in absolute and relative kidney weights were seen in the treated groups. Dose-dependent progressions were present in the female population.

Compound-related nephropathy was also observed in the kidneys of mice during this study. The nephropathy was characterized by the presence of multiple foci of renal tubular regeneration, sometimes in conjunction with interstitial lymphocytic infiltrates and/or foci of interstitial fibrosis. The severity of these lesions were minimal or mild in all cases. Interstitial lymphocytic infiltrates were seen without signs of renal tubular regeneration, these lesions were considered not compound-related. The incidence of renal tubular regeneration in female mice did indicate dose

dependency, but this progression was not evident in the male mice.

Although nephropathy was seen in the control group at a relatively low incidence (6/40 mice, 15%), increasing incidence was observed in Study Group III (8/40 mice, 20%) and a greater incidence was seen in Group IV (19/40 mice, 47.5%).

The histopathologic changes in conjunction with the absolute and relative organ weight data provides supportive evidence of renal morphological changes, but definative clinical pathological evidence of renal insufficiency was not present.

Absolute and relative liver weights of treated mice were increased in a dose-response progression (with the exception of lower Study Group II male absolute liver weights). This treatment related effect of increased absolute liver weights was found to be statistically significant in female mice of Study Group IV. Relative liver weights were found to be significantly ($P \leq 0.01$) increased in male and female mice of study Group IV and only female mice of study Group III.

Although no histopathologic lesions were found which clarify the manifestations of the grossly increased liver weights, decreased serum albumin levels of treated male mice of Study Groups III and IV were noted, possibly indicating limited hepatic impairment. In consideration of the relative severity of these changes there is no positive correlation between the greatest hepatic organ weight changes (seen in treated female mice) and the greatest decreases in albumin levels (seen in treated male mice). Therefore it is probable that alternate mechanisms are responsible for the decreased albumin values and hepatic weight changes.

V. Conclusion

Pyrene given orally to mice for 13 weeks caused compound-related effects in all treated dose levels (75, 125, and 250 mg/kg/day). No compound-related mortality could be attributed to pyrene administration during this study.

The compound related effects seen in the low dose group (75 mg/kg/day) were limited to salavation, mildly increased total food consumption (females only) and mildly reduced total weight gains which in combination

produced increased food conversion ratios. Hematology evaluation yielded minor numerical decreases in RBC, PCV and HGB values in male mice only. Compound related statistically significant decreases in absolute and relative kidney weights (males) were noted. Corresponding lesions of renal tubular regeneration (nephropathy) were noted on histopathologic evaluation. Nephropathy was noted in 4 of 40 mice (10.0%) of this group with severity ranging from minimal to mild. Absolute liver weights were found to be mildly increased in both sexes with female mice possessing increases in relative liver weights also.

Mid dose (125 mg/kg/day) mice had compound-related effects limited to salivation, significantly elevated food consumption (Study week 8, female mice), increased total food consumption (females) and slighty decreased total weight gain (males and females). Food conversion ratios were therefore increased above control values. Group III male mice also had numerical decreases in RBC, PCV and HGB values. Male mice also had significant decreases in serum albumin at the week 14 evaluation. Significant decreases in absolute and relative kidney weights were noted. Microscopic lesions of renal tubular regeneration were noted in 8 of 40 mice (20.0%)

of this group. Severity of this lesion ranged from minimal to mild. Absolute and relative liver weights were increased in mice of both sexes.

Study Group IV (250 mg/kg/day) female mice had compound-related salivation, significant food consumption increases during 5 of the 13 weeks on study and an increased total food consumption. Total food consumption was dramatically increased (13.1%) in female mice compared to a lesser effect in males (2.7%). Mice of both sexes had reduced total weight gains causing increased food conversion ratios. Statistically significant decreases in RBC, PCV and HGB values were seen in male mice of Study Group IV with females exhibiting only slight decreases in these parameters. Male mice had significant decreases in serum albumin at the week 14 evaluation. Highly significant decreases in absolute and relative kidney weights were seen in both male and female mice. Renal tubular regeneration (nephropathy) was evident in 19 of 40 mice (47.5%) of this group. Severity of the nepropathy from minimal to mild. Statistically significant increased absolute liver weights were seen in female mice of this group with numerically increased absolute liver weights observed in the male population.

Relative liver weights were significantly increased in mice of both sexes.

Due to the pyrene effects seen in the 75 mg/kg/day dose level it must be concluded that the no effect dose level is less than 75 mg/kg/day.

Table 1.

Mouse Oral 13 Week Subchronic Toxicity
Study of Pyrene
Incidence of Clinical Effects
(number of affected animals/ number of live animals)

TRL Study #042-012

	MALES				FEMALES			
Group	I	II	III	IV	I	II	III	IV
Dose Level (mg/kg/day)	0	75	125	250	0	75	125	250
Week 1								
Salivation	--	2/20	2/20	3/20	1/20	--	2/20	5/20
Week 2								
Salivation	--	3/20	2/20	3/20	--	3/20	3/20	6/20
Axillary mass	--	1/20	--	--	1/20	2/20	--	--
Urine wet abdomen	--	1/20	--	1/20	--	1/20	--	--
Hypoactive	--	1/20	--	--	--	2/20	2/20	--
Labored respiration	--	1/20	--	--	--	--	--	--
Dead	--	1/20	1/20	--	--	2/20	2/20	--
Unkempt appearance	--	--	--	--	--	--	--	4/20
Week 3								
Salivation	--	5/19	5/19	7/20	--	3/18	2/18	9/20
Axillary mass	--	--	--	--	1/20	--	--	--
Urine wet abdomen	--	1/19	--	--	--	--	--	--
Week 4								
Salivation	--	8/19	9/19	6/20	--	5/18	7/18	5/20
Axillary mass	--	--	--	--	1/20	--	--	--
Exophthalmos	--	--	--	--	1/20	--	--	--
Inguinal mass	1/20	--	--	--	--	--	--	--

-- No animal in group affected by given sign.

Table 1. (con't)

Mouse Oral 13 Week Subchronic Toxicity
Study of Pyrene
Incidence of Clinical Effects
(number of affected animals/ number of live animals)

TRL Study #042-012

	MALES				FEMALES			
Group	I	II	III	IV	I	II	III	IV
Dose Level (mg/kg/day)	0	75	125	250	0	75	125	250
Week 5								
Salivation	--	8/18	4/19	6/20	--	6/18	2/18	9/20
Axillary mass	--	--	--	--	1/20	--	--	--
Exophthalmos	--	--	--	--	1/20	--	--	--
Inguinal mass	1/20	--	--	--	--	--	--	--
Atrophy eye	--	--	--	--	1/20	--	--	--
Week 6								
Salivation	--	4/19	4/19	6/20	--	4/18	3/18	5/20
Axillary mass	--	--	--	--	1/20	--	--	--
Inguinal mass	1/20	--	--	--	--	--	--	--
Atrophy eye	--	--	--	--	1/20	--	--	--
Week 7								
Salivation	--	--	1/19	3/20	--	1/19	4/18	4/20
Axillary mass	--	--	--	--	1/20	--	--	--
Inguinal mass	1/20	--	--	--	--	--	--	--
Atrophy eye	--	--	--	--	1/20	--	--	--
Swollen penis	1/20	--	--	--				
Superficial wound	1/20	--	1/19	--	--	--	--	--

-- No animal in group affected by given sign.

Table 1. (con't)

Mouse Oral 13 Week Subchronic Toxicity
Study of Pyrene
Incidence of Clinical Effects
(number of affected animals/ number of live animals)

TRL Study #042-012

	MALES				FEMALES			
Group	I	II	III	IV	I	II	III	IV
Dose Level (mg/kg/day)	0	75	125	250	0	75	125	250
Week 8								
Salivation	--	8/19	0/19	0/20	--	6/18	2/18	4/20
Axillary mass	--	--	--	--	1/20	--	--	--
Inguinal mass	1/20	--	--	--	--	--	--	--
Atrophy eye	--	--	--	--	1/20	--	--	--
Swollen penis	1/20	--	--	--				
Superficial wound	1/20	--	1/19	--	--	--	--	--
Week 9								
Salivation	--	4/19	1/19	5/20	--	2/18	2/18	5/20
Axillary mass	--	--	--	--	1/20	--	--	--
Atrophy eye	--	--	--	--	1/20	--	--	--
Swollen penis	1/20	--	--	--				
Superficial wound	1/20	--	1/19	--	--	--	--	--
Week 10								
Salivation	--	3/19	1/19	4/20	--	4/18	1/18	3/20
Inguinal mass	1/20	--	--	--	--	--	--	--
Atrophy eye	--	--	--	--	1/20	--	--	--
Swollen penis	1/20	--	--	--				
Superficial wound	1/20	--	--	--	--	--	1/19	--
Exophthalmos	--	--	--	--	1/20	--	--	--
Alopecia	--	--	--	--	--	1/18	--	--
Pale	--	1/19	--	--	--	--	--	--

-- No animal in group affected by given sign.

Table 1. (con't)

Mouse Oral 13 Week Subchronic Toxicity
Study of Pyrene
Incidence of Clinical Effects
(number of affected animals/ number of live animals)

TRL Study #042-012

	MALES				FEMALES			
Group	I	II	III	IV	I	II	III	IV
Dose Level (mg/kg/day)	0	75	125	250	0	75	125	250
Week 11								
Salivation	--	3/18	--	1/20	--	4/18	1/18	3/20
Inguinal mass	1/20	--	--	--	--	--	--	--
Atrophy eye	--	--	--	--	1/20	--	--	--
Swollen penis	1/20	--	--	--				
Superficial wound	1/20	--	1/19	--	--	--	--	--
Exophthalmos	--	--	--	--	1/20	--	--	--
Alopecia	--	--	--	--	--	1/18	--	--
Pale	--	1/19	--	--	--	--	--	--
Hypothermic	--	1/19	--	--	--	--	--	--
Hypoactive	--	1/19	--	--	--	--	--	--
Dead	--	1/19	--	--	--	--	--	--
Week 12								
Salivation	--	4/18	1/19	0/20	--	4/18	2/18	--
Inguinal mass	1/20	--	--	--	--	--	--	--
Atrophy eye	--	--	--	--	2/20	--	--	--
Swollen penis	1/20	--	--	--				
Superficial wound	1/20	--	1/19	--	--	--	--	--
Alopecia	--	--	--	--	--	1/18	--	--
Week 13								
Salivation	--	2/18	1/19	3/20	--	2/18	2/18	1/20
Inguinal mass	1/20	--	--	--	--	--	--	--
Atrophy eye	--	--	--	--	2/20	--	--	--
Swollen penis	1/20	--	--	--				
Superficial wound	1/20	--	1/19	--	--	--	--	--
Alopecia	--	--	--	--	--	1/18	--	--

-- No animal in group affected by given sign.

Table 2.

Mouse Oral 13 Week Subchronic Toxicity Study of Pyrene

Group Mean Body Weight, Weight Change, and Food Consumption in grams

TRL Study #042-012

	MALES				FEMALES			
Group	I	II	III	IV	I	II	III	IV
Dose Level (mg/kg/day)	Control	75	125	250	Control	75	125	250
Initial								
Body Weight	26.0	26.0	26.2	26.3	21.6	21.5	21.4	21.6
Pretreatment								
Body Weight	29.1	29.3	29.3	29.2	23.6	23.7	23.7	23.4
Weight Change	+3.1	+3.3	+3.1	+2.9	+2.0	+2.2	+2.3	+1.8
Food Consumption	36.3	37.3	36.6	36.4	33.4	33.9	33.7	33.5
Week 1								
Body Weight	29.7	29.4	30.0	29.7	24.3	23.7	23.7	23.9
Weight Change	+0.6	+0.1	+0.7	+0.5	+0.7	0.0	0.0	+0.5
Food Consumption	31.3	32.7	32.2	33.1	30.5	31.5	30.7	35.2
Week 2								
Body Weight	30.3	30.2	29.8	30.2	24.6	24.3	24.5	24.4
Weight Change	+0.6	+0.8	-0.2	+0.5	+0.3	+0.6	+0.8	+0.5
Food Consumption	30.7	30.4	30.7	31.6	30.9	30.9	31.4	35.5
Week 3								
Body Weight	31.1	30.6	30.7	30.5	25.5	25.2	24.7	25.2
Weight Change	+0.8	+0.4	+0.9	+0.3	+0.9	+0.9	+0.2	+0.8
Food Consumption	29.3	27.7	27.8	29.7	29.8	30.0	29.4	35.9**

* Significant at $p \leq 0.05$ versus Control Group I
** Significant at $p \leq 0.01$ versus Control Group I

Table 2.(con't)

Mouse Oral 13 Week Subchronic Toxicity Study of Pyrene

Group Mean Body Weight, Weight Change, and Food Consumption in grams

TRL Study #042-012

	MALES				FEMALES			
Group	I	II	III	IV	I	II	III	IV
Dose Level (mg/kg/day)	Control	75	125	250	Control	75	125	250
Week 4								
Body Weight	31.6	31.0	31.2	31.0	26.2	25.8	25.6	25.9
Weight Change	+0.5	+0.4	+0.5	+0.5	+0.7	+0.6	+0.9	+0.7
Food Consumption	28.1	28.1	28.5	30.2	29.4	28.9	29.6	37.1**
Week 5								
Body Weight	32.4	31.6	32.0	31.8	26.7	26.4	26.5	26.4
Weight Change	+0.8	+0.6	+0.8	+0.8	+0.5	+0.6	+0.9	+0.5
Food Consumption	29.4	28.2	29.6	30.7	30.4	30.1	32.4	33.5
Week 6								
Body Weight	33.0	32.0	32.6	32.1	26.8	26.8	26.9	26.7
Weight Change	+0.6	+0.4	+0.6	+0.3	+0.1	+0.4	+0.4	+0.3
Food Consumption	29.2	27.5	28.9	29.9	29.1	29.0	31.3	31.9
Week 7								
Body Weight	33.1	32.2	32.8	32.5	26.9	26.6	27.1	26.6
Weight Change	+0.1	+0.2	+0.2	+0.4	+0.1	-0.2	+0.2	-0.1
Food Consumption	27.8	27.5	27.5	29.2	27.8	27.9	31.2	31.7

* Significant at $p \leq 0.05$ versus Control Group I
** Significant at $p \leq 0.01$ versus Control Group I

Table 2.(con't)

Mouse Oral 13 Week Subchronic Toxicity Study of Pyrene

Group Mean Body Weight, Weight Change, and Food Consumption in grams

TRL Study #042-012

	MALES				FEMALES			
Group	I	II	III	IV	I	II	III	IV
Dose Level (mg/kg/day)	Control	75	125	250	Control	75	125	250
Week 8								
Body Weight	34.0	32.9	33.4	33.1	27.2	26.9	27.9	27.3
Weight Change	+0.9	+0.7	+0.6	+0.6	+0.3	+0.3	+0.8	+0.7
Food Consumption	30.8	27.8*	28.7	30.3	28.5	28.9	31.3*	31.8*
Week 9								
Body Weight	33.8	32.8	33.5	33.3	27.7	27.2	27.5	27.2
Weight Change	-0.2	-0.1	+0.1	+0.2	+0.5	+0.3	-0.4	-0.1
Food Consumption	27.9	25.6	27.2	28.9	26.6	27.4	29.0	29.9**
Week 10								
Body Weight	34.4	33.1	33.9	33.8	27.6	27.7	27.8	27.6
Weight Change	+0.6	+0.3	+0.4	+0.5	-0.1	+0.5	+0.3	+0.4
Food Consumption	29.0	26.7*	29.2	29.4	28.6	30.3	30.9	31.9*
Week 11								
Body Weight	34.7	33.4	34.2	34.0	27.9	27.8	28.5	27.7
Weight Change	+0.3	+0.3	+0.3	+0.2	+0.3	+0.1	+0.7	+0.1
Food Consumption	28.8	26.8	28.0	29.2	27.7	28.5	29.2	30.0

* Significant at $p \leq 0.05$ versus Control Group I
** Significant at $p \leq 0.01$ versus Control Group I

Table 2.(con't)

Mouse Oral 13 Week Subchronic Toxicity Study of Pyrene

Group Mean Body Weight, Weight Change, and Food Consumption in grams

TRL Study #042-012

	MALES				FEMALES			
Group	I	II	III	IV	I	II	III	IV
Dose Level (mg/kg/day)	Control	75	125	250	Control	75	125	250
Week 12								
Body Weight	35.0	33.5	34.5	34.1	28.3	28.0	28.4	27.9
Weight Change	+0.3	+0.1	+0.3	+0.1	+0.4	+0.2	-0.1	+0.2
Food Consumption	28.9	27.1	28.8	29.2	28.9	28.6	31.3	30.8
Week 13								
Body Weight	34.9	33.7	34.0	34.1	28.4	28.1	28.2	27.9
Weight Change	-0.1	+0.2	-0.5	0.0	+0.1	+0.1	-0.2	0.0
Food Consumption	26.7	24.5	25.9	26.6	26.6	27.1	28.0	28.7
Total Food Consumption[1]	377.9	360.6	373.0	388.0	374.8	379.1	395.7	423.9
Total Weight Gain[1]	5.8	4.4	4.7	4.9	4.8	4.4	4.5	4.5
Food Conversion Ratio[2]	65.2	82.0	79.4	79.2	78.1	86.2	87.9	94.2

1 Total food consumption and total weight gain values are based on values from Study Week 1 through Study Week 13.
2 Grams of food consumed /grams of body weight gained during the study
* Significant at $p \leq 0.05$ versus Control Group I
** Significant at $p \leq 0.01$ versus Control Group I

Table

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Summary

TRL Study #042-012 MALES Week of Test Pretreatment

	RBC $x10^6$/ul	PCV %	HGB g/dl	WBC $x10^3$/ul	MCV fl	MCH pg	MCHC g/dl
Group V							
Mean	6.09	33.5	12.7	7.4	55.8	20.9	37.9
S.D.	1.02	5.40	2.11	1.33	1.6	1.75	2.72

FEMALES

	RBC $x10^6$/ul	PCV %	HGB g/dl	WBC $x10^3$/ul	MCV fl	MCH pg	MCHC g/dl
Group V							
Mean	6.57	36.3	13.7	8.5	55.9	20.9	37.8
S.D.	0.86	5.03	1.53	1.89	1.9	1.10	1.71

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Summary - Differential

TRL Study #042-012 MALES Week of Test Pretreatment

	WBC $x10^3/ul$	ABS. NEUT. $x10^3/ul$	ABS. LYMPH. $x10^3/ul$	ABS. MONO. $x10^3/ul$	ABS. EO. $x10^3/ul$	ABS. BASO. $x10^3/ul$
Group V						
Mean	7.4	0.8	6.5	0.1	0.0	0.0
S.D.	1.33	0.43	1.44	0.13	0.07	0.00

FEMALES

	WBC $x10^3/ul$	ABS. NEUT. $x10^3/ul$	ABS. LYMPH. $x10^3/ul$	ABS. MONO. $x10^3/ul$	ABS. EO. $x10^3/ul$	ABS. BASO. $x10^3/ul$
Group V						
Mean	8.5	1.2	7.1	0.1	0.2	0.0
S.D.	1.89	0.39	1.70	0.10	0.14	0.00

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 MALES Week of Test Pretreatment

ANIMAL NUMBER	CHOL	LDH	Na	K	Cl	TCO_2
	mg/dl	U/l	meq/l	meq/l	mmol/l	mmol/l
Group V	Baseline					
221	106.7	93.2	153.2	9.80	112.5	32.5
222	124.5	105.1	150.5	10.74	110.6	30.2
223	136.8	106.7	151.8	13.66	109.0	34.1
224	146.0	112.9	149.2	12.66	108.2	31.3
225	127.1	232.5	152.5	14.84	110.4	33.6
226	100.7	243.5	150.6	12.42	113.1	28.6
227	109.9	254.0	150.7	8.75	107.9	35.6
228	127.4	136.0	152.2	9.54	110.0	32.8
229	115.5	205.5	149.7	11.30	105.1	35.7
230	123.6	183.9	151.1	11.18	109.1	34.4
Mean	121.8	167.3	151.2	11.49	109.6	32.9
S.D.	13.88	63.49	1.26	1.92	2.31	2.30

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 FEMALES Week of Test Pretreatment

ANIMAL NUMBER	GLUC mg/dl	BUN mg/dl	TP g/dl	ALB g/dl	GLOB g/dl	A/G
Group V	Baseline					
241	269.6	28.1	5.60	3.21	2.39	1.34
242	312.5	28.8	5.40	3.04	2.36	1.29
243	292.9	27.0	5.28	3.01	2.27	1.33
244	289.7	24.4	5.52	3.11	2.41	1.29
245	299.5	24.6	5.41	2.95	2.46	1.20
246	286.3	20.1	5.22	2.99	2.23	1.34
247	263.0	17.8	5.53	3.19	2.34	1.36
248	412.6	22.2	5.11	3.00	2.11	1.42
249	273.9	24.4	5.08	2.88	2.20	1.31
250	315.9	23.3	5.52	3.05	2.47	1.23
Mean	301.6	24.1	5.37	3.04	2.32	1.31
S.D.	42.66	3.45	0.19	0.10	0.12	0.06

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Summary - Differential

TRL Study #042-012 MALES Week of Test Pretreatment

	WBC $x10^3/ul$	NEUT NON SEG %	NEUT SEG %	LYMPH %	MONO %	EO %	BASO %
Group V							
Mean	7.4	0.0	10.9	87.4	1.0	0.7	0.0
S.D.	1.33	0.00	6.09	7.33	1.58	1.12	0.00

FEMALES

	WBC $x10^3/ul$	NEUT NON SEG %	NEUT SEG %	LYMPH %	MONO %	EO %	BASO %
Group V							
Mean	8.5	0.0	14.4	82.7	0.8	2.1	0.0
S.D.	1.89	0.00	4.12	4.16	1.03	1.45	0.00

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Summary

TRL Study #042-012 MALES Week of Test 14

	RBC $x10^6$/ul	PCV %	HGB g/dl	WBC $x10^3$/ul	MCV fl	MCH pg	MCHC g/dl
Group I							
Mean	8.51	45.1	14.3	7.5	53.5	16.8	31.8
S.D.	0.41	2.05	0.55	1.83	1.5	0.77	1.17
Group II							
Mean	8.41	44.3	13.9	7.1	53.1	16.6	31.5
S.D.	0.73	3.89	0.97	2.35	1.8	0.98	1.52
Group III							
Mean	8.39	44.1	13.8	7.6	53.0	16.4	31.2
S.D.	0.27	1.20	0.66	2.18	0.9	0.59	1.03
Group IV							
Mean	7.69**	40.5**	12.9**	8.3	53.4	16.9	32.0
S.D.	0.48	2.03	0.50	2.55	1.6	0.72	0.84

FEMALES

	RBC $x10^6$/ul	PCV %	HGB g/dl	WBC $x10^3$/ul	MCV fl	MCH pg	MCHC g/dl
Group I							
Mean	8.65	45.7	14.4	5.2	53.4	16.7	31.6
S.D.	0.68	3.73	0.72	0.87	2.0	0.82	1.55
Group II							
Mean	7.94**	43.3	13.9	6.2	55.2*	17.5	32.2
S.D.	0.49	2.85	0.87	2.00	1.0	0.84	1.60
Group III							
Mean	8.34	44.4	14.3	5.5	53.9	17.3	32.3
S.D.	0.40	1.43	0.49	2.04	1.0	1.10	1.42
Group IV							
Mean	8.19	43.4	13.8	6.7	53.6	16.8	31.8
S.D.	0.36	2.28	0.61	2.00	1.6	0.63	1.36

* P less than or equal to 0.05
** P less than or equal to 0.01

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Summary - Differential

TRL Study #042-012 MALES Week of Test 14

	WBC $x10^3/ul$	ABS. NEUT. $x10^3/ul$	ABS. LYMPH. $x10^3/ul$	ABS. MONO. $x10^3/ul$	ABS. EO. $x10^3/ul$	ABS. BASO. $x10^3/ul$
Group I						
Mean	7.5	1.2	6.0	0.1	0.2	0.0
S.D.	1.83	0.53	1.33	0.05	0.19	0.00
Group II						
Mean	7.1	0.8	6.0	0.1	0.1	0.0
S.D.	2.35	0.64	1.87	0.13	0.14	0.00
Group III						
Mean	7.6	0.8	6.4	0.2	0.2	0.0
S.D.	2.18	0.39	1.95	0.17	0.14	0.00
Group IV						
Mean	8.3	0.8	7.3	0.2	0.1	0.0
S.D.	2.55	0.30	2.44	0.24	0.13	0.00

FEMALES

	WBC $x10^3/ul$	ABS. NEUT. $x10^3/ul$	ABS. LYMPH. $x10^3/ul$	ABS. MONO. $x10^3/ul$	ABS. EO. $x10^3/ul$	ABS. BASO. $x10^3/ul$
Group I						
Mean	5.2	0.6	4.3	0.2	0.1	0.0
S.D.	0.87	0.30	0.66	0.18	0.09	0.00
Group II						
Mean	6.2	1.0	5.1	0.1	0.1	0.0
S.D.	2.00	0.49	1.57	0.07	0.17	0.00
Group III						
Mean	5.5	0.7	4.5	0.2	0.1	0.0
S.D.	2.04	0.55	1.75	0.11	0.12	0.00
Group IV						
Mean	6.7	0.7	5.8	0.1	0.1	0.0
S.D.	2.00	0.42	1.62	0.16	0.11	0.00

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Summary - Differential

TRL Study #042-012 MALES Week of Test 14

	WBC $x10^3/ul$	NEUT NON SEG %	NEUT SEG %	LYMPH %	MONO %	EO %	BASO %
Group I							
Mean	7.5	0.0	15.2	80.7	2.0	2.1	0.0
S.D.	1.83	0.00	6.05	6.95	0.94	1.73	0.00
Group II							
Mean	7.1	0.0	11.5	85.8	1.2	1.5	0.0
S.D.	2.35	0.00	5.23	5.35	1.40	1.35	0.00
Group III							
Mean	7.6	0.0	11.3	83.9	2.5	2.3	0.0
S.D.	2.18	0.00	4.85	6.82	2.17	1.89	0.00
Group IV							
Mean	8.3	0.0	10.4	86.5	2.4	0.7	0.0
S.D.	2.55	0.00	4.25	5.02	2.59	1.34	0.00

FEMALES

	WBC $x10^3/ul$	NEUT NON SEG %	NEUT SEG %	LYMPH %	MONO %	EO %	BASO %
Group I							
Mean	5.2	0.0	11.2	84.4	3.0	1.4	0.0
S.D.	0.87	0.00	5.01	7.14	3.50	1.71	0.00
Group II							
Mean	6.2	0.0	14.9	81.9	1.5	1.7	0.0
S.D.	2.00	0.00	6.95	7.06	1.08	1.95	0.00
Group III							
Mean	5.5	0.0	13.0	81.7	3.0	2.3	0.0
S.D.	2.04	0.00	7.12	8.08	1.56	2.45	0.00
Group IV							
Mean	6.7	0.0	10.3	86.3	2.0	1.4	0.0
S.D.	2.00	0.00	4.24	4.85	1.89	1.17	0.00

Table

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Summary

TRL Study #042-012 MALES Week of Test Pretreatment

	GLUC mg/dl	BUN mg/dl	TP g/dl	ALB g/dl	GLOB g/dl	A/G
Group V						
Mean	380.2	25.6	5.42	2.88	2.55	1.13
S.D.	36.43	4.22	0.30	0.14	0.19	0.07

FEMALES

	GLUC mg/dl	BUN mg/dl	TP g/dl	ALB g/dl	GLOB g/dl	A/G
Group V						
Mean	301.6	24.1	5.37	3.04	2.32	1.31
S.D.	42.66	3.45	0.19	0.10	0.12	0.06

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Summary

TRL Study #042-012 MALES Week of Test Pretreatment

	TOT BILI	ALK PHOS	SGOT	SGPT
	mg/dl	U/l	U/l	U/l
Group V				
Mean	0.22	89.0	59.8	24.4
S.D.	0.07	13.09	19.01	4.39

FEMALES

	TOT BILI	ALK PHOS	SGOT	SGPT
	mg/dl	U/l	U/l	U/l
Group V				
Mean	0.20	104.5	62.2	25.3
S.D.	0.04	22.09	12.67	7.96

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 MALES Week of Test 14

ANIMAL NUMBER	TOT BILI	ALK PHOS	SGOT	SGPT
	mg/dl	U/l	U/l	U/l
Group III	125 mg/kg/day			
101	0.12	37.6	44.3	22.9
102	0.09	36.6	53.4	I
103	0.15	28.9	44.8	I
104	0.10	27.4	82.6	50.4
105	0.13	33.4	47.4	22.3
106	0.14	82.0	45.5	24.4
107	0.24	29.6	44.1	21.1
108	0.19	35.2	44.9	19.1
109	0.41	28.2	47.5	25.5
111[a]				
Mean	0.17	37.7	50.5	26.5
S.D.	0.10	17.06	12.38	10.73
Group IV	250 mg/kg/day			
151	0.13	44.5	39.6	21.8
152	0.14	37.0	46.8	29.0
153	0.09	22.6	58.8	29.2
154	0.05	36.4	77.4	I
155	0.18	57.3	57.4	25.6
156	0.13	25.4	28.1	17.0
157	0.18	29.2	58.8	23.3
158[a]				
159	0.00	39.6	31.3	16.7
160[a]				
Mean	0.11	36.5	49.8	23.2
S.D.	0.06	11.19	16.51	5.13

[a] Unable to obtain specimen
I Insufficient specimen, unable to perform test

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 MALES Week of Test 14

ANIMAL NUMBER	TOT BILI	ALK PHOS	SGOT	SGPT
	mg/dl	U/l	U/l	U/l
Group I	0 mg/kg/day			
1	0.27	25.9	S	20.1
2	I	I	I	I
3	0.18	96.2	41.6	I
4	0.23	44.4	40.1	23.8
5	0.05	54.5	50.1	27.6
6	0.18	36.8	42.0	20.2
7	0.12	23.3	52.7	34.5
8	0.28	45.8	144.2	0.0
9	0.16	36.8	I	I
10	0.05	25.2	33.9	18.6
Mean	0.17	43.2	57.8	24.1
S.D.	0.08	22.49	38.62	6.03
Group II	75 mg/kg/day			
51	0.20	33.9	I	I
52	0.09	30.5	7.8	14.9
53	0.18	25.0	I	I
54	0.02	27.3	47.4	24.0
55	0.12	57.7	I	I
56	0.13	23.0	I	I
57	0.20	34.0	45.2	23.3
58	0.14	42.8	40.5	21.2
59	0.03	37.5	37.9	19.8
60	0.38	18.6	69.7	47.7
Mean	0.15	33.0	41.4	25.2
S.D.	0.10	11.25	19.97	11.51

S S.D. too high, insufficient specimen to repeat test
I Insufficient specimen, unable to perform test

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 MALES Week of Test 14

ANIMAL NUMBER	GLUC mg/dl	BUN mg/dl	TP g/dl	ALB g/dl	GLOB g/dl	A/G
Group III	125 mg/kg/day					
101	201.5	17.3	5.73	3.03	2.70	1.12
102	170.6	18.8	4.86	2.80	2.06	1.36
103	205.2	23.2	5.32	2.82	2.50	1.13
104	242.1	23.5	5.16	2.70	2.46	1.10
105	213.7	25.5	5.62	2.95	2.67	1.10
106	212.9	24.5	5.52	2.61	2.91	0.90
107	188.3	23.4	5.09	2.56	2.53	1.01
108	163.4	16.8	5.46	2.87	2.59	1.11
109	164.5	27.4	5.99	3.15	2.84	1.11
111[a]						
Mean	195.8	22.3	5.42	2.83*	2.58	1.10
S.D.	26.45	3.74	0.35	0.19	0.25	0.12
Group IV	250 mg/kg/day					
151	253.6	17.5	5.54	2.71	2.83	0.96
152	225.2	25.7	5.89	3.05	2.84	1.07
153	273.9	24.9	5.67	2.80	2.87	0.98
154	228.2	23.2	5.19	2.87	2.32	1.24
155	212.7	22.4	5.86	2.82	3.04	0.93
156	181.2	18.6	5.21	2.69	2.52	1.07
157	248.7	23.4	4.92	2.80	2.12	1.32
158[a]						
159	201.8	22.1	5.18	2.91	2.27	1.28
160[a]						
Mean	228.2	22.2	5.43	2.83*	2.60	1.11
S.D.	30.02	2.86	0.36	0.11	0.34	0.15

* P less than or equal to 0.05

[a] Unable to obtain specimen

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 MALES Week of Test 14

ANIMAL NUMBER	GLUC mg/dl	BUN mg/dl	TP g/dl	ALB g/dl	GLOB g/dl	A/G
Group I	0 mg/kg/day					
1	202.6	22.0	5.56	2.94	2.62	1.12
2	289.5	17.8	5.57	I	I	I
3	213.2	18.3	5.66	3.11	2.55	1.22
4	316.7	23.6	5.86	3.18	2.68	1.19
5	218.2	25.1	5.82	3.00	2.82	1.06
6	253.2	18.5	6.07	3.13	2.94	1.06
7	228.1	31.8	6.04	3.08	2.96	1.04
8	264.9	23.3	5.63	3.09	2.54	1.22
9	277.5	24.9	5.94	3.30	2.64	1.25
10	185.3	20.7	5.30	2.85	2.45	1.16
Mean	244.9	22.6	5.75	3.08	2.69	1.15
S.D.	42.19	4.22	0.24	0.13	0.18	0.08
Group II	75 mg/kg/day					
51	206.1	20.1	5.31	2.76	2.55	1.08
52	254.6	16.2	5.57	3.06	2.51	1.22
53	232.9	20.7	5.50	2.92	2.58	1.13
54	244.9	20.3	5.65	3.09	2.56	1.21
55	188.4	21.1	5.10	2.69	2.41	1.12
56	209.3	17.3	5.51	2.67	2.84	0.94
57	242.5	19.9	5.82	3.04	2.78	1.09
58	223.5	28.1	6.03	3.32	2.71	1.23
59	210.0	22.0	5.54	2.74	2.80	0.98
60	412.1	25.8	6.00	3.06	2.94	1.04
Mean	242.4	21.2	5.60	2.94	2.67	1.10
S.D.	63.05	3.55	0.29	0.21	0.17	0.10

I Insufficient specimen, unable to perform test

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values - Differential

TRL Study #042-012 FEMALES Week of Test 14

ANIMAL NUMBER	WBC $x10^3/ul$	ABS. NEUT. $x10^3/ul$	ABS. LYMPH. $x10^3/ul$	ABS. MONO. $x10^3/ul$	ABS. EO. $x10^3/ul$	ABS. BASO. $x10^3/ul$
Group III	125 mg/kg/day					
126	6.0	0.7	5.3	0.0	0.0	0.0
127	3.1	0.3	2.6	0.0	0.1	0.0
128	8.1	0.6	7.0	0.3	0.2	0.0
129	4.6	1.1	3.3	0.1	0.1	0.0
130	8.2	0.7	7.4	0.2	0.0	0.0
131	4.8	0.7	3.6	0.1	0.4	0.0
132	3.7	0.3	3.3	0.2	0.0	0.0
133	4.9	0.7	3.8	0.2	0.2	0.0
134	3.2	0.2	2.8	0.1	0.1	0.0
135	8.2	2.1	5.7	0.3	0.1	0.0
Mean	5.5	0.7	4.5	0.2	0.1	0.0
S.D.	2.04	0.55	1.75	0.11	0.12	0.00
Group IV	250 mg/kg/day					
176	8.5	1.4	7.0	0.1	0.0	0.0
177	8.7	1.4	6.7	0.3	0.3	0.0
178	4.2	0.3	3.8	0.1	0.0	0.0
179	7.4	0.2	7.0	0.0	0.2	0.0
180	4.6	0.6	3.9	0.1	0.0	0.0
181	5.3	0.6	4.5	0.1	0.2	0.0
182	8.1	0.9	7.1	0.0	0.1	0.0
183	8.4	0.7	7.1	0.5	0.1	0.0
184	8.1	0.7	7.0	0.2	0.1	0.0
185	3.7	0.3	3.4	0.0	0.0	0.0
Mean	6.7	0.7	5.8	0.1	0.1	0.0
S.D.	2.00	0.42	1.62	0.16	0.11	0.00

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values - Differential

TRL Study #042-012 FEMALES Week of Test 14

ANIMAL NUMBER	WBC $x10^3/ul$	ABS. NEUT. $x10^3/ul$	ABS. LYMPH. $x10^3/ul$	ABS. MONO. $x10^3/ul$	ABS. EO. $x10^3/ul$	ABS. BASO. $x10^3/ul$
Group I	0 mg/kg/day					
26	4.9	0.9	3.9	0.1	0.0	0.0
27	3.4	0.1	3.2	0.1	0.0	0.0
28	5.4	0.3	4.8	0.1	0.2	0.0
29	5.5	0.7	4.6	0.0	0.2	0.0
30	4.0	0.3	3.7	0.0	0.0	0.0
31	5.9	0.6	5.2	0.1	0.0	0.0
32	6.1	0.6	5.1	0.3	0.1	0.0
33	5.9	1.1	4.5	0.1	0.2	0.0
34	5.4	0.6	4.6	0.1	0.0	0.0
35	5.4	0.8	3.8	0.6	0.1	0.0
Mean	5.2	0.6	4.3	0.2	0.1	0.0
S.D.	0.87	0.30	0.66	0.18	0.09	0.00
Group II	75 mg/kg/day					
76	5.6	1.7	3.8	0.1	0.0	0.0
77	7.7	1.3	6.1	0.0	0.3	0.0
78	5.5	0.3	5.2	0.1	0.0	0.0
80	3.3	0.5	2.8	0.1	0.0	0.0
81	6.2	1.1	5.0	0.2	0.0	0.0
82	5.1	0.6	4.4	0.0	0.1	0.0
83	6.4	1.2	5.1	0.2	0.0	0.0
84	7.3	0.7	6.3	0.1	0.2	0.0
85	10.6	1.6	8.4	0.1	0.5	0.0
86	4.6	0.6	3.9	0.0	0.1	0.0
Mean	6.2	1.0	5.1	0.1	0.1	0.0
S.D.	2.00	0.49	1.57	0.07	0.17	0.00

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values

TRL Study #042-012 FEMALES Week of Test 14

ANIMAL NUMBER	RBC $x10^6$/ul	PCV %	HGB g/dl	WBC $x10^3$/ul	MCV fl	MCH pg	MCHC g/dl
Group III	125 mg/kg/day						
126	8.40	45.2	14.9	6.0	54	17.7	33.0
127	8.21	44.6	14.6	3.1	55	17.8	32.7
128	8.14	44.0	14.0	8.1	54	17.2	31.8
129	8.43	44.4	14.3	4.6	53	17.0	32.2
130	8.52	45.3	14.9	8.2	54	17.5	32.9
131	8.48	45.3	14.0	4.8	54	16.5	30.9
132	8.27	43.3	13.4	3.7	53	16.2	30.9
133	8.56	44.5	14.0	4.9	53	16.4	31.5
134	8.95	46.5	14.6	3.2	53	16.3	31.4
135	7.40	41.2	14.7	8.2	56	19.9	35.7
Mean	8.34	44.4	14.3	5.5	53.9	17.3	32.3
S.D.	0.40	1.43	0.49	2.04	1.0	1.10	1.42
Group IV	250 mg/kg/day						
176	7.83	41.4	14.2	8.5	53	18.1	34.3
177	8.18	43.0	13.3	8.7	53	16.3	30.9
178	8.76	48.4	14.5	4.2	56	16.6	30.0
179	8.82	44.2	14.4	7.4	51	16.3	32.6
180	7.91	42.8	13.3	4.6	55	16.8	31.1
181	8.17	45.2	14.4	5.3	56	17.6	31.9
182	8.20	44.1	13.6	8.1	54	16.6	30.8
183	8.28	42.9	13.6	8.4	53	16.4	31.7
184	8.03	41.3	13.9	8.1	52	17.3	33.7
185	7.73	40.5	12.6	3.7	53	16.3	31.1
Mean	8.19	43.4	13.8	6.7	53.6	16.8	31.8
S.D.	0.36	2.28	0.61	2.00	1.6	0.63	1.36

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values

TRL Study #042-012 FEMALES Week of Test 14

ANIMAL NUMBER	RBC $x10^6$/ul	PCV %	HGB g/dl	WBC $x10^3$/ul	MCV fl	MCH pg	MCHC g/dl
Group I	0 mg/kg/day						
26	9.51	49.2	15.3	4.9	52	16.1	31.1
27	8.46	46.0	13.9	3.4	55	16.4	30.2
28	9.38	48.6	14.6	5.4	52	15.6	30.0
29	8.94	45.1	15.0	5.5	51	16.8	33.3
30	8.96	49.9	14.9	4.0	56	16.6	29.9
31	7.75	41.1	13.8	5.9	54	17.8	33.6
32	7.35	38.0	13.0	6.1	52	17.7	34.2
33	8.50	47.3	14.8	5.9	56	17.4	31.3
34	8.95	44.7	13.9	5.4	51	15.5	31.1
35	8.66	47.3	14.9	5.4	55	17.2	31.5
Mean	8.65	45.7	14.4	5.2	53.4	16.7	31.6
S.D.	0.68	3.73	0.72	0.87	2.0	0.82	1.55
Group II	75 mg/kg/day						
76	8.61	47.8	14.9	5.6	56	17.3	31.2
77	7.21	39.8	12.8	7.7	56	17.8	32.2
78	7.62	41.7	15.0	5.5	55	19.7	36.0
80	7.94	43.9	13.3	3.3	56	16.8	30.3
81	7.35	38.4	12.7	6.2	53	17.3	33.1
82	7.97	43.1	14.1	5.1	55	17.7	32.7
83	8.43	45.5	14.5	6.4	55	17.2	31.9
84	7.72	42.5	13.6	7.3	56	17.6	32.0
85	7.96	44.0	13.4	10.6	56	16.8	30.5
86	8.63	46.1	14.8	4.6	54	17.1	32.1
Mean	7.94**	43.3	13.9	6.2	55.2*	17.5	32.2
S.D.	0.49	2.85	0.87	2.00	1.0	0.84	1.60

* P less than or equal to 0.05
** P less than or equal to 0.01

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values - Differential

TRL Study #042-012 FEMALES Week of Test 14

ANIMAL NUMBER	WBC	NEUT NON SEG	NEUT SEG	LYMPH	MONO	EO	BASO	COMMENT
	$x10^3/ul$	%	%	%	%	%	%	
Group III 125 mg/kg/day								
126	6.0	0	11	89	0	0	0	
127	3.1	0	11	85	1	3	0	
128	8.1	0	8	86	4	2	0	
129	4.6	0	24	71	3	2	0	
130	8.2	0	8	90	2	0	0	
131	4.8	0	15	74	3	8	0	
132	3.7	0	7	88	5	0	0	
133	4.9	0	15	77	4	4	0	
134	3.2	0	5	88	4	3	0	
135	8.2	0	26	69	4	1	0	
Mean	5.5	0.0	13.0	81.7	3.0	2.3	0.0	
S.D.	2.04	0.00	7.12	8.08	1.56	2.45	0.00	
Group IV 250 mg/kg/day								
176	8.5	0	17	82	1	0	0	
177	8.7	0	16	77	4	3	0	
178	4.2	0	7	90	2	1	0	
179	7.4	0	3	94	0	3	0	
180	4.6	0	13	84	2	1	0	
181	5.3	0	11	85	1	3	0	
182	8.1	0	11	88	0	1	0	
183	8.4	0	8	85	6	1	0	
184	8.1	0	9	87	3	1	0	
185	3.7	0	8	91	1	0	0	
Mean	6.7	0.0	10.3	86.3	2.0	1.4	0.0	
S.D.	2.00	0.00	4.24	4.85	1.89	1.17	0.00	

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values - Differential

TRL Study #042-012 FEMALES Week of Test 14

ANIMAL NUMBER	WBC	NEUT NON SEG	NEUT SEG	LYMPH	MONO	EO	BASO	COMMENT
	$x10^3$/ul	%	%	%	%	%	%	
Group I	0 mg/kg/day							
26	4.9	0	18	79	3	0	0	
27	3.4	0	3	94	3	0	0	
28	5.4	0	6	88	2	4	0	
29	5.5	0	13	84	0	3	0	
30	4.0	0	7	93	0	0	0	
31	5.9	0	10	88	2	0	0	
32	6.1	0	10	84	5	1	0	
33	5.9	0	18	77	1	4	0	
34	5.4	0	12	86	2	0	0	
35	5.4	0	15	71	12	2	0	
Mean	5.2	0.0	11.2	84.4	3.0	1.4	0.0	
S.D.	0.87	0.00	5.01	7.14	3.50	1.71	0.00	
Group II	75 mg/kg/day							
76	5.6	0	31	67	2	0	0	
77	7.7	0	17	79	0	4	0	
78	5.5	0	5	94	1	0	0	
80	3.3	0	14	84	2	0	0	
81	6.2	0	17	80	3	0	0	
82	5.1	0	11	87	0	2	0	
83	6.4	0	18	79	3	0	0	
84	7.3	0	9	86	2	3	0	
85	10.6	0	15	79	1	5	0	
86	4.6	0	12	84	1	3	0	
Mean	6.2	0.0	14.9	81.9	1.5	1.7	0.0	
S.D.	2.00	0.00	6.95	7.06	1.08	1.95	0.00	

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values - Differential

TRL Study #042-012 MALES Week of Test 14

ANIMAL NUMBER	WBC	NEUT NON SEG	NEUT SEG	LYMPH	MONO	EO	BASO	COMMENT
	$x10^3$/ul	%	%	%	%	%	%	
Group III	125 mg/kg/day							
101	7.4	0	8	87	0	5	0	
102	6.8	0	17	71	7	5	0	
103	8.9	0	5	94	1	0	0	
104	5.7	0	6	90	3	1	0	
105	7.2	0	7	90	2	1	0	
106	8.0	0	15	80	5	0	0	
107	10.3	0	14	82	2	2	0	
108	8.3	0	12	84	0	4	0	
109	3.1	0	19	77	2	2	0	
111	10.5	0	10	84	3	3	0	
Mean	7.6	0.0	11.3	83.9	2.5	2.3	0.0	
S.D.	2.18	0.00	4.85	6.82	2.17	1.89	0.00	
Group IV	250 mg/kg/day							
151	10.6	0	4	94	1	1	0	
152	5.7	0	10	88	2	0	0	
153	7.3	0	8	90	2	0	0	
154	12.4	0	12	87	1	0	0	
155	4.6	0	19	81	0	0	0	
156	7.5	0	11	89	0	0	0	
157	9.3	0	10	83	3	4	0	
158	11.2	0	5	92	3	0	0	
159	6.1	0	13	82	3	2	0	
160	8.5	0	12	79	9	0	0	
Mean	8.3	0.0	10.4	86.5	2.4	0.7	0.0	
S.D.	2.55	0.00	4.25	5.02	2.59	1.34	0.00	

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values - Differential

TRL Study #042-012 MALES Week of Test 14

ANIMAL NUMBER	WBC	NEUT NON SEG	NEUT SEG	LYMPH	MONO	EO	BASO	COMMENT
	$x10^3$/ul	%	%	%	%	%	%	
Group I	0 mg/kg/day							
1	8.1	0	17	78	3	2	0	
2	5.3	0	2	96	2	0	0	
3	9.8	0	18	76	2	4	0	
4	7.0	0	23	75	1	1	0	
5	11.3	0	16	78	1	5	0	
6	7.6	0	10	88	2	0	0	
7	6.4	0	22	75	1	2	0	
8	6.0	0	17	75	4	4	0	
9	6.6	0	14	82	2	2	0	
10	6.7	0	13	84	2	1	0	
Mean	7.5	0.0	15.2	80.7	2.0	2.1	0.0	
S.D.	1.83	0.00	6.05	6.95	0.94	1.73	0.00	
Group II	75 mg/kg/day							
51	10.6	0	7	88	0	5	0	
52	7.0	0	9	89	1	1	0	
53	8.4	0	14	85	0	1	0	
54	6.8	0	13	86	0	1	0	
55	10.5	0	24	72	4	0	0	
56	4.5	0	13	84	1	2	0	
57	5.7	0	6	91	1	2	0	
58	3.3	0	12	85	2	1	0	
59	7.8	0	10	89	0	1	0	
60	6.4	0	7	89	3	1	0	
Mean	7.1	0.0	11.5	85.8	1.2	1.5	0.0	
S.D.	2.35	0.00	5.23	5.35	1.40	1.35	0.00	

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values - Differential

TRL Study #042-012 MALES Week of Test 14

ANIMAL NUMBER	WBC $x10^3/ul$	ABS. NEUT. $x10^3/ul$	ABS. LYMPH. $x10^3/ul$	ABS. MONO. $x10^3/ul$	ABS. EO. $x10^3/ul$	ABS. BASO. $x10^3/ul$
Group III	125 mg/kg/day					
101	7.4	0.6	6.4	0.0	0.4	0.0
102	6.8	1.2	4.8	0.5	0.3	0.0
103	8.9	0.4	8.4	0.1	0.0	0.0
104	5.7	0.3	5.1	0.2	0.1	0.0
105	7.2	0.5	6.5	0.1	0.1	0.0
106	8.0	1.2	6.4	0.4	0.0	0.0
107	10.3	1.4	8.4	0.2	0.2	0.0
108	8.3	1.0	7.0	0.0	0.3	0.0
109	3.1	0.6	2.4	0.1	0.1	0.0
111	10.5	1.1	8.8	0.3	0.3	0.0
Mean	7.6	0.8	6.4	0.2	0.2	0.0
S.D.	2.18	0.39	1.95	0.17	0.14	0.00
Group IV	250 mg/kg/day					
151	10.6	0.4	10.0	0.1	0.1	0.0
152	5.7	0.6	5.0	0.1	0.0	0.0
153	7.3	0.6	6.6	0.1	0.0	0.0
154	12.4	1.5	10.8	0.1	0.0	0.0
155	4.6	0.9	3.7	0.0	0.0	0.0
156	7.5	0.8	6.7	0.0	0.0	0.0
157	9.3	0.9	7.7	0.3	0.4	0.0
158	11.2	0.6	10.3	0.3	0.0	0.0
159	6.1	0.8	5.0	0.2	0.1	0.0
160	8.5	1.0	6.7	0.8	0.0	0.0
Mean	8.3	0.8	7.3	0.2	0.1	0.0
S.D.	2.55	0.30	2.44	0.24	0.13	0.00

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values - Differential

TRL Study #042-012 MALES Week of Test 14

ANIMAL NUMBER	WBC $x10^3/ul$	ABS. NEUT. $x10^3/ul$	ABS. LYMPH. $x10^3/ul$	ABS. MONO. $x10^3/ul$	ABS. EO. $x10^3/ul$	ABS. BASO. $x10^3/ul$
Group I	0 mg/kg/day					
1	8.1	1.4	6.3	0.2	0.2	0.0
2	5.3	0.1	5.1	0.1	0.0	0.0
3	9.8	1.8	7.4	0.2	0.4	0.0
4	7.0	1.6	5.3	0.1	0.1	0.0
5	11.3	1.8	8.8	0.1	0.6	0.0
6	7.6	0.8	6.7	0.2	0.0	0.0
7	6.4	1.4	4.8	0.1	0.1	0.0
8	6.0	1.0	4.5	0.2	0.2	0.0
9	6.6	0.9	5.4	0.1	0.1	0.0
10	6.7	0.9	5.6	0.1	0.1	0.0
Mean	7.5	1.2	6.0	0.1	0.2	0.0
S.D.	1.83	0.53	1.33	0.05	0.19	0.00
Group II	75 mg/kg/day					
51	10.6	0.7	9.3	0.0	0.5	0.0
52	7.0	0.6	6.2	0.1	0.1	0.0
53	8.4	1.2	7.1	0.0	0.1	0.0
54	6.8	0.9	5.8	0.0	0.1	0.0
55	10.5	2.5	7.6	0.4	0.0	0.0
56	4.5	0.6	3.8	0.0	0.1	0.0
57	5.7	0.3	5.2	0.1	0.1	0.0
58	3.3	0.4	2.8	0.1	0.0	0.0
59	7.8	0.8	6.9	0.0	0.1	0.0
60	6.4	0.4	5.7	0.2	0.1	0.0
Mean	7.1	0.8	6.0	0.1	0.1	0.0
S.D.	2.35	0.64	1.87	0.13	0.14	0.00

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values

TRL Study #042-012 MALES Week of Test 14

ANIMAL NUMBER	RBC $x10^6$/ul	PCV %	HGB g/dl	WBC $x10^3$/ul	MCV fl	MCH pg	MCHC g/dl
Group III	125 mg/kg/day						
101	8.93	45.4	13.9	7.4	51	15.6	30.6
102	8.53	44.9	13.8	6.8	53	16.2	30.7
103	8.27	44.3	13.7	8.9	54	16.6	30.9
104	8.26	43.9	14.4	5.7	54	17.4	32.8
105	8.61	45.9	15.0	7.2	53	17.4	32.7
106	8.19	43.0	13.1	8.0	53	16.0	30.5
107	8.11	43.6	13.1	10.3	54	16.2	30.0
108	8.43	44.3	13.7	8.3	53	16.3	30.9
109	8.02	41.7	12.8	3.1	53	16.0	30.7
111	8.55	43.7	14.2	10.5	52	16.6	32.5
Mean	8.39	44.1	13.8	7.6	53.0	16.4	31.2
S.D.	0.27	1.20	0.66	2.18	0.9	0.59	1.03
Group IV	250 mg/kg/day						
151	8.23	43.9	13.9	10.6	54	16.9	31.7
152	7.52	41.2	12.8	5.7	55	17.0	31.1
153	7.83	39.8	12.4	7.3	52	15.8	31.2
154	6.89	38.0	12.5	12.4	56	18.1	32.9
155	7.73	41.4	13.3	4.6	54	17.2	32.1
156	7.86	40.4	13.2	7.5	52	16.8	32.7
157	7.02	37.2	12.3	9.3	54	17.5	33.1
158	8.49	42.9	13.3	11.2	51	15.7	31.0
159	7.67	39.6	13.0	6.1	52	16.9	32.8
160	7.61	40.4	12.6	8.5	54	16.6	31.2
Mean	7.69**	40.5**	12.9**	8.3	53.4	16.9	32.0
S.D.	0.48	2.03	0.50	2.55	1.6	0.72	0.84

** P less than or equal to 0.01

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values

TRL Study #042-012 MALES Week of Test 14

ANIMAL NUMBER	RBC $x10^6$/ul	PCV %	HGB g/dl	WBC $x10^3$/ul	MCV fl	MCH pg	MCHC g/dl
Group I	0 mg/kg/day						
1	8.71	47.1	14.8	8.1	54	17.0	31.4
2	7.92	43.2	14.0	5.3	55	17.7	32.4
3	8.46	47.1	14.8	9.8	56	17.5	31.4
4	8.73	45.5	13.6	7.0	53	15.6	29.9
5	8.31	42.0	14.1	11.3	51	17.0	33.6
6	8.56	45.6	14.9	7.6	54	17.4	32.7
7	8.95	46.1	15.0	6.4	52	16.8	32.5
8	9.03	46.1	14.1	6.0	52	15.6	30.6
9	8.70	46.3	14.1	6.6	54	16.2	30.5
10	7.76	41.5	13.5	6.7	54	17.4	32.5
Mean	8.51	45.1	14.3	7.5	53.5	16.8	31.8
S.D.	0.41	2.05	0.55	1.83	1.5	0.77	1.17
Group II	75 mg/kg/day						
51	7.73	40.5	12.4	10.6	53	16.0	30.6
52	7.27	39.3	13.4	7.0	54	18.4	34.1
53	8.69	46.4	13.7	8.4	54	15.8	29.5
54	8.24	43.4	14.5	6.8	53	17.6	33.4
55	9.54	50.3	15.7	10.5	53	16.5	31.2
56	8.40	41.6	13.1	4.5	50	15.6	31.5
57	7.67	42.9	13.4	5.7	56	17.5	31.2
58	8.98	45.0	13.8	3.3	51	15.4	30.7
59	8.29	42.8	14.0	7.8	52	16.9	32.7
60	9.29	50.9	15.1	6.4	55	16.3	29.7
Mean	8.41	44.3	13.9	7.1	53.1	16.6	31.5
S.D.	0.73	3.89	0.97	2.35	1.8	0.98	1.52

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 FEMALES Week of Test Pretreatment

ANIMAL NUMBER	CHOL	LDH	Na	K	Cl	TCO_2
	mg/dl	U/l	meq/l	meq/l	mmol/l	mmol/l
Group V	Baseline					
251	96.6	113.5	149.7	13.48	112.5	30.4
252	104.2	92.3	150.8	9.98	111.1	30.6
253	116.8	117.9	151.0	10.36	109.2	34.4
254	98.1	113.3	149.4	13.14	114.4	31.0
255	100.8	103.5	151.0	10.80	112.3	30.1
256	100.1	119.6	150.5	13.26	113.1	29.0
257	86.0	80.4	149.2	12.74	112.4	34.0
258	95.9	187.1	150.5	13.24	113.1	30.6
259	118.2	118.2	153.8	10.74	112.9	33.3
260	87.8	106.8	149.9	13.38	115.2	31.2
Mean	100.5	115.3	150.6	12.11	112.6	31.5
S.D.	10.58	28.20	1.30	1.44	1.65	1.80

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 FEMALES Week of Test Pretreatment

ANIMAL NUMBER	TOT BILI	ALK PHOS	SGOT	SGPT
	mg/dl	U/l	U/l	U/l
Group V	Baseline			
241	0.16	137.5	50.2	23.5
242	0.24	98.7	68.6	25.4
243	0.20	114.2	79.0	46.0
244	0.20	89.9	63.7	24.7
245	0.27	134.2	80.9	29.5
246	0.22	103.1	53.7	18.6
247	0.22	76.3	56.9	24.2
248	0.23	111.0	45.5	22.3
249	0.12	110.4	72.6	19.6
250	0.16	69.8	50.4	19.5
Mean	0.20	104.5	62.2	25.3
S.D.	0.04	22.09	12.67	7.96

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 MALES Week of Test Pretreatment

ANIMAL NUMBER	TOT BILI	ALK PHOS	SGOT	SGPT
	mg/dl	U/l	U/l	U/l
Group V	Baseline			
211	0.17	82.3	39.3	22.9
212	0.22	78.8	57.8	30.2
213	0.20	90.6	49.0	18.9
214	0.19	92.0	62.9	20.9
215	0.22	117.0	44.2	25.4
216	0.34	92.8	84.8	20.1
217	0.21	86.1	54.0	23.0
218	0.23	85.7	49.6	23.3
219	0.11	66.8	56.0	27.3
220	0.32	97.4	100.8	32.4
Mean	0.22	89.0	59.8	24.4
S.D.	0.07	13.09	19.01	4.39

Table

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 MALES Week of Test Pretreatment

ANIMAL NUMBER	GLUC mg/dl	BUN mg/dl	TP g/dl	ALB g/dl	GLOB g/dl	A/G
Group V	Baseline					
211	352.0	21.8	5.48	2.88	2.60	1.11
212	366.0	25.9	5.66	2.92	2.74	1.07
213	334.0	26.9	5.60	2.95	2.65	1.11
214	327.0	24.1	5.85	3.07	2.78	1.10
215	381.9	31.8	5.39	2.75	2.64	1.04
216	397.0	29.8	5.59	3.04	2.55	1.19
217	420.0	21.6	4.87	2.64	2.23	1.18
218	387.5	31.3	5.12	2.87	2.25	1.28
219	442.5	22.9	5.54	2.92	2.62	1.11
220	393.7	20.1	5.14	2.72	2.42	1.12
Mean	380.2	25.6	5.42	2.88	2.55	1.13
S.D.	36.43	4.22	0.30	0.14	0.19	0.07

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values - Differential

TRL Study #042-012 FEMALES Week of Test Pretreatment

ANIMAL NUMBER	WBC	NEUT NON SEG	NEUT SEG	LYMPH	MONO	EO	BASO	COMMENT
	$x10^3/ul$	%	%	%	%	%	%	
Group V	Baseline							
231	6.7	0	18	82	0	0	0	occ HJB
232	7.3	0	18	81	0	1	0	rare HJB
233	9.3	0	10	85	0	5	0	rare HJB
234	8.4	0	16	82	0	2	0	many HJB
235	8.9	0	21	73	3	3	0	many HJB
236	12.5	0	9	88	1	2	0	occ HJB
237	6.7	0	11	85	1	3	0	occ HJB
238	6.3	0	11	87	1	1	0	many HJB
239	9.3	0	13	82	2	3	0	occ HJB
240	9.9	0	17	82	0	1	0	occ HJB
Mean	8.5	0.0	14.4	82.7	0.8	2.1	0.0	
S.D.	1.89	0.00	4.12	4.16	1.03	1.45	0.00	

HJB - Hoewll-Jolly Bodies
occ - occasional

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values - Differential

TRL Study #042-012 FEMALES Week of Test Pretreatment

ANIMAL NUMBER	WBC $x10^3/ul$	ABS. NEUT. $x10^3/ul$	ABS. LYMPH. $x10^3/ul$	ABS. MONO. $x10^3/ul$	ABS. EO. $x10^3/ul$	ABS. BASO. $x10^3/ul$
Group V	Baseline					
231	6.7	1.2	5.5	0.0	0.0	0.0
232	7.3	1.3	5.9	0.0	0.1	0.0
233	9.3	0.9	7.9	0.0	0.5	0.0
234	8.4	1.3	6.9	0.0	0.2	0.0
235	8.9	1.9	6.5	0.3	0.3	0.0
236	12.5	1.1	11.0	0.1	0.3	0.0
237	6.7	0.7	5.7	0.1	0.2	0.0
238	6.3	0.7	5.5	0.1	0.1	0.0
239	9.3	1.2	7.6	0.2	0.3	0.0
240	9.9	1.7	8.1	0.0	0.1	0.0
Mean	8.5	1.2	7.1	0.1	0.2	0.0
S.D.	1.89	0.39	1.70	0.10	0.14	0.00

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values

TRL Study #042-012 FEMALES Week of Test Pretreatment

ANIMAL NUMBER	RBC $x10^6$/ul	PCV %	HGB g/dl	WBC $x10^3$/ul	MCV fl	MCH pg	MCHC g/dl
Group V	Baseline						
231	6.38	34.0	12.8	6.7	54	20.1	37.6
232	7.88	43.3	15.3	7.3	56	19.4	35.3
233	6.46	36.1	13.2	9.3	56	20.4	36.6
234	7.47	42.3	15.3	8.4	57	20.5	36.2
235	7.05	37.2	13.6	8.9	53	19.3	36.6
236	4.99	28.1	11.1	12.5	57	22.2	39.5
237	6.51	35.1	13.9	6.7	55	21.4	39.6
238	5.67	31.5	11.9	6.3	56	21.0	37.8
239	6.10	33.2	13.5	9.3	55	22.1	40.7
240	7.15	42.2	15.9	9.9	60	22.2	37.7
Mean	6.57	36.3	13.7	8.5	55.9	20.9	37.8
S.D.	0.86	5.03	1.53	1.89	1.9	1.10	1.71

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values - Differential

TRL Study #042-012 MALES Week of Test Pretreatment

ANIMAL NUMBER	WBC	NEUT NON SEG	NEUT SEG	LYMPH	MONO	EO	BASO	COMMENT
	$x10^3/ul$	%	%	%	%	%	%	
Group V	Baseline							
201[a]								
202	4.8	0	12	88	0	0	0	many HJB;mod P
203	9.1	0	3	96	1	0	0	
204	6.6	0	17	82	1	0	0	many HJB
205	9.0	0	7	92	1	0	0	many HJB
206	7.5	0	8	92	0	0	0	
207	6.9	0	18	78	1	3	0	occ HJB
208	7.8	0	7	92	0	1	0	many HJB
209	6.9	0	6	92	0	2	0	occ HJB
210	8.2	0	20	75	5	0	0	
Mean	7.4	0.0	10.9	87.4	1.0	0.7	0.0	
S.D.	1.33	0.00	6.09	7.33	1.58	1.12	0.00	

[a] Specimen clotted

HJB - Howell-Jolly Bodies
P - polychromasia
mod - moderate
occ - occasional

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values - Differential

TRL Study #042-012 MALES Week of Test Pretreatment

ANIMAL NUMBER	WBC $x10^3/ul$	ABS. NEUT. $x10^3/ul$	ABS. LYMPH. $x10^3/ul$	ABS. MONO. $x10^3/ul$	ABS. EO. $x10^3/ul$	ABS. BASO. $x10^3/ul$
Group V	Baseline					
201[a]						
202	4.8	0.6	4.2	0.0	0.0	0.0
203	9.1	0.3	8.7	0.1	0.0	0.0
204	6.6	1.1	5.4	0.1	0.0	0.0
205	9.0	0.6	8.3	0.1	0.0	0.0
206	7.5	0.6	6.9	0.0	0.0	0.0
207	6.9	1.2	5.4	0.1	0.2	0.0
208	7.8	0.5	7.2	0.0	0.1	0.0
209	6.9	0.4	6.3	0.0	0.1	0.0
210	8.2	1.6	6.2	0.4	0.0	0.0
Mean	7.4	0.8	6.5	0.1	0.0	0.0
S.D.	1.33	0.43	1.44	0.13	0.07	0.00

[a] Specimen clotted

Table

Mouse Oral Subchronic Toxicity Study of Pyrene

Hematology Values

TRL Study #042-012 MALES Week of Test Pretreatment

ANIMAL NUMBER	RBC $x10^6$/ul	PCV %	HGB g/dl	WBC $x10^3$/ul	MCV fl	MCH pg	MCHC g/dl
Group V	Baseline						
201[a]							
202	3.91	21.4	7.7	4.8	55	19.7	36.0
203	6.41	34.9	12.3	9.1	55	19.2	35.2
204	6.06	32.8	11.9	6.6	55	19.6	36.3
205	7.18	39.6	14.1	9.0	56	19.6	35.6
206	7.48	40.3	14.9	7.5	55	19.9	37.0
207	6.18	33.7	13.1	6.9	55	21.2	38.9
208	5.68	33.3	12.6	7.8	59	22.2	37.8
209	5.69	32.7	13.8	6.9	58	24.3	42.2
210	6.22	33.0	14.0	8.2	54	22.5	42.4
Mean	6.09	33.5	12.7	7.4	55.8	20.9	37.9
S.D.	1.02	5.40	2.11	1.33	1.6	1.75	2.72

[a] Specimen clotted

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Summary

TRL Study #042-012 MALES Week of Test 14

	CHOL	LDH	Na	K	Cl	TCO_2
	mg/dl	U/l	meq/l	meq/l	mmol/l	mmol/l
Group I						
Mean	131.4	117.7	154.0	10.25	115.5	32.0
S.D.	17.85	54.94	1.70	1.11	1.42	2.97
Group II						
Mean	131.8	118.7	152.5	9.82	115.4	32.1
S.D.	27.79	115.84	1.14	0.86	1.41	3.71
Group III						
Mean	146.6	111.3	152.2	10.08	114.1	32.9
S.D.	22.08	96.51	1.90	1.62	2.15	2.10
Group IV						
Mean	139.8	92.2	153.9	9.77	115.6	31.6
S.D.	31.54	41.01	1.68	1.20	2.03	1.61

FEMALES

	CHOL	LDH	Na	K	Cl	TCO_2
	mg/dl	U/l	meq/l	meq/l	mmol/l	mmol/l
Group I						
Mean	109.0	117.1	153.1	9.20	115.6	32.6
S.D.	20.04	66.60	1.24	0.77	1.75	4.22
Group II						
Mean	100.7	98.6	153.0	10.21	116.9	32.3
S.D.	20.35	21.83	1.57	0.54	1.09	2.04
Group III						
Mean	140.7*	100.1	154.5	8.98	116.9	32.0
S.D.	34.36	23.84	2.34	1.35	1.83	2.15
Group IV						
Mean	113.8	99.4	153.0	9.56	117.5*	32.2
S.D.	13.69	44.75	2.05	1.03	1.09	2.77

* P less than or equal to 0.05

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Summary

TRL Study #042-012 MALES Week of Test 14

	TOT BILI	ALK PHOS	SGOT	SGPT
	mg/dl	U/l	U/l	U/l
Group I				
Mean	0.17	43.2	57.8	24.1
S.D.	0.08	22.49	38.62	6.03
Group II				
Mean	0.15	33.0	41.4	25.2
S.D.	0.10	11.25	19.97	11.51
Group III				
Mean	0.17	37.7	50.5	26.5
S.D.	0.10	17.06	12.38	10.73
Group IV				
Mean	0.11	36.5	49.8	23.2
S.D.	0.06	11.19	16.51	5.13

FEMALES

	TOT BILI	ALK PHOS	SGOT	SGPT
	mg/dl	U/l	U/l	U/l
Group I				
Mean	0.19	50.8	82.9	24.4
S.D.	0.06	21.35	58.55	11.87
Group II				
Mean	0.15	47.6	74.2	29.2
S.D.	0.10	4.11	39.25	9.33
Group III				
Mean	0.06*	53.6	51.6	27.5
S.D.	0.08	14.32	11.41	10.93
Group IV				
Mean	0.17	60.3	60.6	24.0
S.D.	0.08	14.94	24.42	5.90

* P less than or equal to 0.05

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Summary

TRL Study #042-012 MALES Week of Test 14

	GLUC mg/dl	BUN mg/dl	TP g/dl	ALB g/dl	GLOB g/dl	A/G
Group I						
Mean	244.9	22.6	5.75	3.08	2.69	1.15
S.D.	42.19	4.22	0.24	0.13	0.18	0.08
Group II						
Mean	242.4	21.2	5.60	2.94	2.67	1.10
S.D.	63.05	3.55	0.29	0.21	0.17	0.10
Group III						
Mean	195.8	22.3	5.42	2.83*	2.58	1.10
S.D.	26.45	3.74	0.35	0.19	0.25	0.12
Group IV						
Mean	228.2	22.2	5.43	2.83*	2.60	1.11
S.D.	30.02	2.86	0.36	0.11	0.34	0.15

FEMALES

	GLUC mg/dl	BUN mg/dl	TP g/dl	ALB g/dl	GLOB g/dl	A/G
Group I						
Mean	208.9	18.7	5.47	3.09	2.38	1.30
S.D.	55.64	4.01	0.21	0.16	0.12	0.09
Group II						
Mean	196.5	18.1	5.55	3.12	2.46	1.27
S.D.	43.51	3.14	0.24	0.13	0.18	0.10
Group III						
Mean	197.1	16.6	5.38	3.07	2.33	1.34
S.D.	59.80	1.80	0.50	0.22	0.37	0.17
Group IV						
Mean	223.3	18.8	5.60	3.07	2.53	1.22
S.D.	80.14	5.38	0.37	0.26	0.21	0.12

* P less than or equal to 0.05

[a] Unable to obtain specimen

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Summary

TRL Study #042-012 MALES Week of Test Pretreatment

	CHOL	LDH	Na	K	Cl	TCO_2
	mg/dl	U/l	meq/l	meq/l	mmol/l	mmol/l
Group V						
Mean	121.8	167.3	151.2	11.49	109.6	32.9
S.D.	13.88	63.49	1.26	1.92	2.31	2.30

FEMALES

	CHOL	LDH	Na	K	Cl	TCO_2
	mg/dl	U/l	meq/l	meq/l	mmol/l	mmol/l
Group V						
Mean	100.5	115.3	150.6	12.11	112.6	31.5
S.D.	10.58	28.20	1.30	1.44	1.65	1.80

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 MALES Week of Test 14

ANIMAL NUMBER	CHOL	LDH	Na	K	Cl	TCO_2
	mg/dl	U/l	meq/l	meq/l	mmol/l	mmol/l
Group I	0 mg/kg/day					
11	113.5	115.9	157.2	8.51	114.7	33.1
12	127.7	254.7	152.5	10.34	114.9	31.4
13	111.0	66.3	154.0	10.00	114.4	33.3
14	112.9	99.1	155.1	11.12	116.8	35.0
15	156.9	154.1	155.1	9.57	112.8	35.2
16	138.4	122.6	152.3	10.08	115.1	32.5
17	118.3	94.2	153.5	12.62	117.3	24.7
18	139.8	62.2	154.3	9.27	115.6	31.8
19	160.0	109.0	151.3	10.26	116.5	30.3
20	135.4	99.0	154.7	10.76	117.1	32.6
Mean	131.4	117.7	154.0	10.25	115.5	32.0
S.D.	17.85	54.94	1.70	1.11	1.42	2.97
Group II	75 mg/kg/day					
61	125.1	126.4	152.5	8.78	114.3	30.0
63	180.5	75.7	154.4	10.14	114.8	37.0
64	168.9	76.2	152.3	9.59	115.5	33.3
65	111.9	45.7	151.5	10.22	116.1	31.3
66	111.0	78.3	154.1	8.41	117.7	28.9
67	107.1	65.1	152.1	10.94	113.7	34.8
69	118.7	399.9	151.3	9.97	116.7	26.1
70	130.8	82.6	152.0	10.52	114.0	35.6
Mean	131.8	118.7	152.5	9.82	115.4	32.1
S.D.	27.79	115.84	1.14	0.86	1.41	3.71

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 MALES Week of Test 14

ANIMAL NUMBER	CHOL	LDH	Na	K	Cl	TCO_2
	mg/dl	U/l	meq/l	meq/l	mmol/l	mmol/l
Group III	125 mg/kg/day					
112	152.5	360.5	152.0	11.19	115.3	30.7
113	130.2	50.7	148.8	13.58	114.8	31.1
114	130.0	131.5	152.3	8.91	112.0	35.9
115	131.2	68.1	151.4	8.13	111.3	33.8
116	160.4	76.1	151.8	9.24	114.0	30.3
117	154.8	58.0	150.5	10.60	112.3	32.3
118	165.4	73.3	155.1	10.34	117.7	35.1
119	112.1	101.2	153.4	9.69	113.0	34.9
120	182.4	82.4	154.1	9.02	116.4	31.7
Mean	146.6	111.3	152.2	10.08	114.1	32.9
S.D.	22.08	96.51	1.90	1.62	2.15	2.10
Group IV	250 mg/kg/day					
161	174.9	94.3	153.0	11.10	116.6	28.6
162	159.4	94.6	154.0	9.97	117.7	32.5
163	161.8	60.4	157.3	7.76	117.0	32.1
164	121.2	56.2	155.3	10.64	118.4	32.1
165	131.7	90.7	155.0	9.11	112.5	33.0
166	127.8	94.2	151.6	9.22	112.5	32.5
167	114.9	50.9	154.0	8.56	116.0	31.6
168	196.7	129.9	153.4	10.82	115.5	28.6
169	106.2	186.5	152.0	9.09	114.1	32.0
170	103.6	64.0	153.0	11.40	116.1	32.6
Mean	139.8	92.2	153.9	9.77	115.6	31.6
S.D.	31.54	41.01	1.68	1.20	2.03	1.61

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 FEMALES Week of Test 14

ANIMAL NUMBER	GLUC mg/dl	BUN mg/dl	TP g/dl	ALB g/dl	GLOB g/dl	A/G
Group I	0 mg/kg/day					
26	158.9	18.6	5.67	3.32	2.35	1.41
27	132.9	18.9	5.60	3.24	2.36	1.37
28	297.2	17.5	5.72	3.13	2.59	1.21
29[a]						
30	206.4	15.4	5.21	2.82	2.39	1.18
31	159.0	21.0	5.15	2.92	2.23	1.31
32	255.5	26.0	5.50	3.01	2.49	1.21
33[a]						
34	229.4	12.3	5.33	3.11	2.22	1.40
35	231.5	19.5	5.55	3.14	2.41	1.30
Mean	208.9	18.7	5.47	3.09	2.38	1.30
S.D.	55.64	4.01	0.21	0.16	0.12	0.09
Group II	75 mg/kg/day					
76	208.8	17.7	5.89	3.20	2.69	1.19
77	163.8	18.6	5.34	I	I	I
78	278.8	17.3	5.61	3.18	2.43	1.31
80	I	I	I	I	I	I
81[a]						
82	147.5	19.3	5.47	3.01	2.46	1.22
83	180.1	25.0	5.67	3.08	2.59	1.19
84	185.5	15.2	5.14	3.02	2.12	1.42
85	238.0	16.2	5.54	3.01	2.53	1.19
86	169.2	15.5	5.77	3.37	2.40	1.40
Mean	196.5	18.1	5.55	3.12	2.46	1.27
S.D.	43.51	3.14	0.24	0.13	0.18	0.10

[a] Unable to obtain specimen
I Insufficient specimen, unable to perform test

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 FEMALES Week of Test 14

ANIMAL NUMBER	GLUC mg/dl	BUN mg/dl	TP g/dl	ALB g/dl	GLOB g/dl	A/G
Group III	125 mg/kg/day					
126	I	I	I	I	I	I
127	225.7	20.4	5.55	3.26	2.29	1.42
128[a]						
129	180.9	15.7	4.95	2.87	2.08	1.38
130	168.2	15.7	5.25	I	I	I
131	328.6	17.4	5.61	2.98	2.63	1.13
132	203.1	15.1	5.87	3.33	2.54	1.31
133	170.4	15.4	4.86	3.01	1.85	1.63
134	141.2	17.4	6.17	3.28	2.89	1.13
135	153.9	15.3	4.78	2.76	2.02	1.37
Mean	196.5	16.6	5.38	3.07	2.33	1.34
S.D.	59.70	1.80	0.50	0.22	0.37	0.17
Group IV	250 mg/kg/day					
176	168.7	13.3	5.57	3.03	2.54	1.19
177	165.1	18.4	5.08	2.88	2.20	1.31
178[a]						
179	247.1	10.2	5.46	3.12	2.34	1.33
180	385.6	23.6	5.84	3.13	2.71	1.15
181	245.4	22.0	6.28	3.58	2.70	1.33
182	164.8	19.3	5.50	2.75	2.75	1.00
183[a]						
184	I	I	I	I	I	I
185	186.6	24.8	5.46	2.98	2.48	1.20
Mean	223.3	18.8	5.60	3.07	2.53	1.22
S.D.	80.14	5.38	0.37	0.26	0.21	0.12

[a] Unable to obtain specimen
I Insufficient specimen, unable to perform test

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 FEMALES Week of Test 14

ANIMAL NUMBER	TOT BILI	ALK PHOS	SGOT	SGPT
	mg/dl	U/l	U/l	U/l
Group I	0 mg/kg/day			
26	0.11	50.9	75.8	20.0
27	0.18	53.9	50.8	17.5
28	0.29	60.0	I	I
29[a]				
30	0.27	88.0	I	I
31	0.13	49.5	49.6	19.8
32	0.15	34.0	185.8	45.6
33[a]				
34	0.16	I	I	I
35	0.21	19.6	52.3	19.3
Mean	0.19	50.8	82.9	24.4
S.D.	0.06	21.35	58.55	11.87
Group II	75 mg/kg/day			
76	0.21	44.0	55.8	22.9
77	I	I	I	I
78	0.15	48.2	153.2	40.8
80	I	I	I	I
81[a]				
82	0.03	42.6	74.0	43.2
83	0.16	54.1	48.6	24.8
84	0.18	50.1	41.0	21.3
85	0.29	44.5	94.8	20.9
86	0.00	49.8	52.2	30.4
Mean	0.15	47.6	74.2	29.2
S.D.	0.10	4.11	39.25	9.33

[a] Unable to obtain specimen
I Insufficient specimen, unable to perform test

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 FEMALES Week of Test 14

ANIMAL NUMBER	TOT BILI	ALK PHOS	SGOT	SGPT
	mg/dl	U/l	U/l	U/l
Group III	125 mg/kg/day			
126	I	I	I	I
127	0.00	70.6	62.1	48.4
128[a]				
129	0.03	48.2	61.2	26.0
130	I	I	I	I
131	0.08	46.3	34.1	I
132	0.11	38.2	52.1	18.3
133	0.01	76.7	58.4	27.9
134	0.21	50.4	I	19.2
135	0.00	44.8	41.8	25.4
Mean	0.06*	53.6	51.6	27.5
S.D.	0.08	14.32	11.41	10.93
Group IV	250 mg/kg/day			
176	0.17	59.4	58.1	18.2
177	0.12	48.5	I	I
178[a]				
179	0.23	86.3	49.0	23.7
180	0.14	44.5	103.0	31.2
181	0.15	56.6	41.6	18.4
182	0.32	I	I	I
183[a]				
184	I	I	I	I
185	0.08	66.4	51.3	28.7
Mean	0.17	60.3	60.6	24.0
S.D.	0.08	14.94	24.42	5.90

* P less than or equal to 0.05

[a] Unable to obtain specimen
I Insufficient specimen, unable to perform test

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 FEMALES Week of Test 14

ANIMAL NUMBER	CHOL	LDH	Na	K	Cl	TCO_2
	mg/dl	U/l	meq/l	meq/l	mmol/l	mmol/l
Group I	0 mg/kg/day					
36	89.8	210.4	151.9	9.72	118.0	26.1
37	96.9	139.4	153.4	9.52	114.7	36.2
38	102.9	111.3	151.9	10.40	114.7	31.8
39	154.4	52.9	153.1	8.16	117.0	29.8
40	114.5	76.5	155.8	7.87	113.7	37.2
41	97.5	249.2	153.2	9.76	118.2	26.7
42	100.3	113.1	152.4	9.10	116.7	30.9
43	102.9	90.9	153.8	8.68	113.2	37.8
44	97.1	85.9	151.6	9.41	115.6	33.6
45	133.2	41.0	153.6	9.37	114.6	35.7
Mean	109.0	117.1	153.1	9.20	115.6	32.6
S.D.	20.04	66.60	1.24	0.77	1.75	4.22
Group II	75 mg/kg/day					
87	123.6	69.9	151.4	10.74	116.1	33.6
88	85.6	106.1	153.8	10.34	118.0	31.5
89	135.7	113.9	153.1	10.72	116.9	32.5
90	90.4	116.3	153.2	10.52	115.3	31.0
91	85.4	95.6	155.6	9.12	116.1	36.6
92	83.9	61.0	151.2	10.26	116.9	32.3
93	88.3	119.1	151.6	9.76	117.1	30.7
95	112.8	106.6	154.4	10.24	118.7	30.3
Mean	100.7	98.6	153.0	10.21	116.9	32.3
S.D.	20.35	21.83	1.57	0.54	1.09	2.04

Table (cont'd.)

Mouse Oral Subchronic Toxicity Study of Pyrene

Serum Chemistry Values

TRL Study #042-012 FEMALES Week of Test 14

ANIMAL NUMBER	CHOL	LDH	Na	K	Cl	TCO_2
	mg/dl	U/l	meq/l	meq/l	mmol/l	mmol/l
Group III	125 mg/kg/day					
136	192.2	130.9	156.9	7.77	114.2	34.3
137	155.7	129.7	154.2	9.33	116.5	32.9
138	113.8	108.8	151.1	10.00	115.6	29.8
139	116.3	78.7	154.8	8.45	117.8	29.4
140	111.9	115.4	158.0	6.75	120.5	30.3
142	190.1	84.4	155.4	9.29	117.0	34.1
143	113.8	75.9	153.2	11.16	117.3	34.4
144	132.0	76.6	152.0	9.05	116.2	30.7
Mean	140.7*	100.1	154.5	8.98	116.9	32.0
S.D.	34.36	23.84	2.34	1.35	1.83	2.15
Group IV	250 mg/kg/day					
186	108.3	44.5	154.3	8.66	117.0	35.9
187	132.3	49.0	150.5	11.74	119.0	32.6
188	118.3	91.3	153.5	9.98	118.0	32.9
189	107.1	133.9	151.1	10.14	118.5	28.1
190	86.8	141.3	153.2	8.17	115.7	34.4
191	102.5	110.0	151.0	9.34	116.6	31.8
192	116.5	69.2	154.2	9.47	117.2	34.9
193	113.4	186.2	150.8	10.30	118.9	28.1
194	131.9	98.8	155.3	9.02	117.6	29.6
195	121.3	69.4	156.2	8.81	116.6	33.7
Mean	113.8	99.4	153.0	9.56	117.5*	32.2
S.D.	13.69	44.75	2.05	1.03	1.09	2.77

* P less than or equal to 0.05

Table 7.

Mouse Oral 13 Week Subchronic Toxicity
Study of Pyrene
Gross Pathologic Observations

TRL Study #042-012

	MALES				FEMALES			
Group	I	II	III	IV	I	II	III	IV
Dose Level (mg/kg/day)	0	75	125	250	0	75	125	250
# Examined	20	20	20	20	20	20	20	20
Penis								
Swollen	1	--	--	--				
Uterus								
Enlarged, bilateral					4	3	2	2
Eye								
Atrophied	--	--	--	--	1	--	--	--
Opaque, smaller	--	--	--	--	1	--	--	--
Skin								
Superficial wound	1	--	1	--	--	--	--	--
Liver								
Enlarged	--	1[1]	--	--	--	--	--	--
Light areas, median and caudate lobes	--	1[1]	--	--	--	--	--	--
Spleen								
Enlarged	--	1[1]	--	--	--	--	--	--

1. Found dead animal
-- No animal in group affected by given sign.

Table 7.(cont.)

Mouse Oral 13 Week Subchronic Toxicity
Study of Pyrene
Gross Pathologic Observations

TRL Study #042-012

Group	MALES				FEMALES			
	I	II	III	IV	I	II	III	IV
Dose Level (mg/kg/day)	0	75	125	250	0	75	125	250
# Examined	20	20	20	20	20	20	20	20
Lungs with bronchi								
Left lobe dark with white areas	--	1_1.	--	--	--	--	--	--
Lymph nodes								
Mandibular red, bilaterally	--	1_1.	--	--	--	--	--	--
Esophagus								
Hole(s)/split	--	1_1.	1_1.	--	2_1.	1_1.	--	--
Thoracic cavity								
Clear fluid/yellow material	--	1_1.	--	--	--	--	1_1.	--
Axillary region								
Mass	--	--	--	--	--	1_1.	1_1.	--
Yellow material between skin and muscle layers	--	1_1.	--	--	--	2_1.	1_1.	--

1. Found dead animal
-- No animal in group affected by given sign.

Table 8

Mouse Oral 13 Week Subchronic Toxicity Study of Pyrene
Absolute Organ Weights

TRL Study #042-012

	MALES				FEMALES			
Group	I	II	III	IV	I	II	III	IV
Dose Level mg/kg/day	Control	75	125	250	Control	75	125	250
BODY WEIGHT (weight in grams)	35.0	33.7	34.3	34.1	28.4	28.1	28.3	27.9
BRAIN (weight in grams)	0.506	0.502	0.500	0.494	0.507	0.511	0.517	0.512
HEART (weight in grams)	0.172	0.172	0.173	0.172	0.150	0.156	0.156	0.154
LIVER (weight in grams)	1.760	1.691	1.806	1.862	1.368	1.468	1.523	1.580 #### ****
SPLEEN (weight in grams)	0.081	0.070	0.076	0.074	0.086	0.089	0.086	0.088
KIDNEYS (weight in grams)	0.681	0.584 #### ****	0.585 #### ****	0.546 #### ****	0.445	0.415	0.407 ****	0.396 #### ****
TESTES (weight in grams)	0.259	0.249	0.247	0.253	--	--	--	--

- Significant at P≤.01
**** - Significant at P≤.05

-- Not applicable

Table 8

Mouse Oral 13 Week Subchronic Toxicity Study of Pyrene
Relative Organ Weights

TRL Study #042-012

Group	MALES				FEMALES			
	I	II	III	IV	I	II	III	IV
Dose Level mg/kg/day	Control	75	125	250	Control	75	125	250
BRAIN (% of body weight)	1.4	1.5	1.5	1.4	1.8	1.8	1.8	1.8
HEART (% of body weight)	0.5	0.5	0.5	0.5	0.5	0.6	0.6	0.6
LIVER (% of body weight)	5.0	5.0	5.3	5.5 #### ****	4.8	5.2	5.4 #### ****	5.7 #### ****
SPLEEN (% of body weight)	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3
KIDNEYS (% of body weight)	1.9	1.7 ****	1.7 #### ****	1.6 #### ****	1.6	1.5	1.4 ****	1.4 #### ****
TESTES (% of body weight)	0.7	0.7	0.7	0.7	--	--	--	--

- Significant at P≤.01
**** - Significant at P≤.05

-- Not applicable

Table 9

Mouse Oral 13 Week Subchronic Toxicity Study of Pyrene
Incidence of Histologic Lesions

TRL Study #042-012

		MALES				FEMALES			
Group		I	II	III	IV	I	II	III	IV
Dose Level mg/kg/day		Control	75	125	250	Control	75	125	250
HEART	# Examined	20	2	1	20	20	2	2	20
Inflammation, chronic, active		0	0	0	0	0	1	0	0
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
AORTA	# Examined	20	2	1	20	20	0	1	20
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
THYMUS	# Examined	19	1	1	18	20	1	2	20
Depletion, lymphoid		0	1	0	0	0	1	1	0
Necrosis, lymphoid		0	0	0	0	0	1	0	0
Congestion		1	0	0	0	0	0	1	0
PITUITARY	# Examined	19	2	1	20	19	2	1	20
Angiectasis		0	0	0	0	1	0	0	0
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
ADRENALS (cortex)	# Examined	20	2	1	20	20	1	2	20
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
ADRENALS (medulla)	# Examined	20	2	1	20	20	1	2	20
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
MANDIBULAR SALIVARY	# Examined	20	2	1	20	19	2	2	20
Leukemia, erythrocytic		0	1	0	0	0	0	0	0

-- Not applicable

Table 9 (con't)

Mouse Oral 13 Week Subchronic Toxicity Study of Pyrene
Incidence of Histologic Lesions

TRL Study #042-012

		MALES				FEMALES			
Group		I	II	III	IV	I	II	III	IV
Dose Level mg/kg/day		Control	75	125	250	Control	75	125	250
LUNGS WITH BRONCHI	# Examined	20	20	20	20	20	20	20	20
Interstitium, inflammation		3	6	5	7	6	5	5	2
Infiltration cells, lymphocytic		4	5	1	3	1	7	0	2
Infiltration cells, histiocytic		0	0	0	0	1	0	0	0
Hemorrage		2	1	1	0	1	0	2	0
Congestion		0	1	0	0	0	2	1	0
Pleura, inflammation, suppurative		0	0	0	0	0	0	1	0
Pleura, inflammation, chronic, active		0	0	0	0	0	1	0	0
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
TRACHEA	# Examined	20	2	0	20	20	1	2	20
No lesion found									
ESOPHAGUS	# Examined	20	2	0	20	20	2	2	20
Inflammation, chronic, active		0	0	0	0	0	1	1	0
Inflammation, suppurative		0	0	0	0	0	1	0	0
Inflammation, chronic		0	0	0	0	0	0	1	0
THYROIDS	# Examined	19	2	1	19	20	2	2	19
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
PARATHYROIDS	# Examined	11	2	0	13	17	1	2	15
No lesion found									
STOMACH - FORE	# Examined	20	2	1	20	20	2	2	20
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
STOMACH - GLANDULAR	# Examined	20	2	1	20	20	2	2	20
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
DUODENUM	# Examined	20	2	1	20	20	2	2	20
Leukemia, erythrocytic		0	1	0	0	0	0	0	0

-- Not applicable

Table 9 (con't)

Mouse Oral 13 Week Subchronic Toxicity Study of Pyrene
Incidence of Histologic Lesions

TRL Study #042-012

		MALES				FEMALES			
Group		I	II	III	IV	I	II	III	IV
Dose Level mg/kg/day		Control	75	125	250	Control	75	125	250
MESENTERIC LYMPH NODE	# Examined	20	2	1	20	20	2	1	20
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
LIVER	# Examined	20	20	20	20	20	20	20	20
Necrosis		1	0	1	0	0	2	0	1
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
Infiltration cells, lymphocytic		1	0	0	0	0	0	0	0
Fibrosis		0	0	0	0	0	0	0	1
Mineralization		0	0	0	0	0	1	0	0
GALL BLADDER	# Examined	19	2	1	20	18	0	0	20
No lesion found									
EYES	# Examined	20	1	1	20	20	1	2	20
Degeneration		0	0	0	0	1	0	0	0
OPTIC NERVES	# Examined	17	0	1	14	11	0	1	15
No lesion found									
MAMMARY GLAND	# Examined	6	0	0	6	17	2	2	18
No lesion found									
SKIN	# Examined	20	2	2	20	20	2	2	20
Inflammation, chronic		0	0	1	0	0	0	0	0
Subcutis, inflammation, chronic		0	1	0	0	0	0	0	0
Subcutis, inflammation, chronic, active		0	0	0	0	0	2	0	0
SKELETAL MUSCLE - THIGH	# Examined	20	2	1	20	20	2	2	20
Leukemia, erythrocytic		0	1	0	0	0	0	0	0

-- Not applicable

Table 9 (con't)

Mouse Oral 13 Week Subchronic Toxicity Study of Pyrene
Incidence of Histologic Lesions

TRL Study #042-012

Group		MALES				FEMALES			
		I	II	III	IV	I	II	III	IV
Dose Level	mg/kg/day	Control	75	125	250	Control	75	125	250
JEJUNUM	# Examined	20	2	1	20	20	2	2	20
No lesion found									
ILEUM	# Examined	20	2	1	20	20	2	2	20
Amyloid		1	0	0	1	0	0	0	0
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
CECUM	# Examined	20	2	1	20	20	2	2	20
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
COLON	# Examined	20	2	1	20	19	2	2	20
No lesion found									
RECTUM	# Examined	20	2	1	20	19	2	2	20
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
KIDNEYS	# Examined	20	20	20	20	20	20	20	20
Nephropathy		4	1	1	9	2	3	7	10
Infiltration cells, lymphocytic		5	0	1	1	0	3	0	0
Cyst		0	0	0	0	0	1	0	0
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
SPLEEN	# Examined	20	2	1	20	20	2	2	20
Hematopoietic cell proliferation		0	0	0	0	1	0	0	1
Hemosiderosis		0	0	0	0	0	0	0	1
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
PANCREAS	# Examined	20	2	1	20	20	2	2	20
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
Accessory spleen		0	0	0	1	0	0	0	0

-- Not applicable

Table 9 (con't)

Mouse Oral 13 Week Subchronic Toxicity Study of Pyrene
Incidence of Histologic Lesions

TRL Study #042-012

Group		MALES				FEMALES			
		I	II	III	IV	I	II	III	IV
Dose Level	mg/kg/day	Control	75	125	250	Control	75	125	250
UTERUS	# Examined	--	--	--	--	20	5	4	20
Dilatation						0	2	1	1
Endometrium- hyperplasia, cystic						1	0	0	1
Edema						1	0	0	0
BONE MARROW (FEMUR)	# Examined	20	2	1	20	20	2	2	20
Congestion		0	0	0	0	0	2	1	0
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
LYMPH NODE (MANDIBULAR)	# Examined	--	1	--	--	--	--	--	--
Leukemia, erythrocytic		--	1	--	--	--	--	--	--
PREPUTIAL GLAND	# Examined	1	--	--	--	--	--	--	--
Abscess		1	--	--	--	--	--	--	--
PENIS	# Examined	1	--	--	--	--	--	--	--
No lesion found									

-- Not applicable

Table 9 (con't)

Mouse Oral 13 Week Subchronic Toxicity Study of Pyrene
Incidence of Histologic Lesions

TRL Study #042-012

		MALES				FEMALES			
Group		I	II	III	IV	I	II	III	IV
Dose Level mg/kg/day		Control	75	125	250	Control	75	125	250
SCIATIC NERVE	# Examined	20	2	1	19	20	2	2	20
No lesion found									
BRAIN	# Examined	20	2	1	20	20	1	2	20
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
SPINAL CORD	# Examined	20	2	1	20	20	2	2	20
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
STERNUM	# Examined	20	2	1	20	20	2	2	20
No lesion found									
URINARY BLADDER	# Examined	20	2	1	20	19	2	2	20
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
SEMINAL VESICLES	# Examined	20	2	1	20	--	--	--	--
No lesion found									
PROSTATE	# Examined	20	2	1	19	--	--	--	--
No lesion found									
TESTES	# Examined	20	2	1	20	--	--	--	--
Leukemia, erythrocytic		0	1	0	0	0	0	0	0
Degeneration		1	0	0	0	0	0	0	0
EPIDIDYMIDES	# Examined	20	2	1	20	--	--	--	--
No lesion found									
OVARIES	# Examined	--	--	--	--	20	2	2	20
Cyst						2	0	0	0

-- Not applicable